UNIVERSITY OF MICHIGAN
JUL 6 1955
MEDICAL LIBRARY

VOL. 18 (New Series) MAY, 1955

JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY

CONTENTS

	Page
Studies in [illegible], Part 3: Visual Fits. W. Ritchie Russell and C. W. M. Whitty	79
The Arterial [illegible] and its Significance. D. H. M. Woollam and J. W. Millen	97
Encephalitis [illegible] Ex-van Bogaert, A. Dubois, P. G. Janssens, J. Radermecker, [illegible] Twenty, and [illegible] Wemmon	103
Observations [illegible] to Cutaneous Thermal Stimuli. P. P. Lele and D. C. Sinclair	120
Chronic Progressive [illegible] Studies. J. E. M. Dutton and G. L. Alexander	125
The Association of [illegible] Encephalopathy Demonstrated Cerebral Atrophy. T. H. Goulby	129
Chorioid Plexus [illegible] Causing Spontaneous Subarachnoid Haemorrhage. J. Ernsting	134
The Use of Dexamethasone [illegible] in Psychiatric Practice. E. B. Strauss and W. A. H. Rogers	137
Ischaemic Sensory [illegible] with Spinal and Cerebral Lesions. R. W. Gilliatt	145
Anxiety and [illegible] to Pain. Malcolm Piercy, Alick Elithorn, R. T. C. Pratt and Margaret Kennedy	155
Book Reviews	163

LONDON
MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

Yearly [illegible] £2 2s. U.S.A. $7.00 SINGLE NUMBER 12s. 6d.

Edited by
RITCHIE RUSSELL

with the assistance of the following Editorial Committee:

E. D. Adrian	G. Jefferson
F. C. Bartlett	Aubrey Lewis
G. L. Brown	A. Meyer
James Bull	R. A. McCance
E. A. [illegible]	D. W. C. Northfield
[illegible] Clark	J. B. Penneybacker
[illegible] Daniel	Dorothy Russell
[illegible] M. Dott	Eliot Slater
M. A. Falconer	C. P. Symonds
A. [illegible]	J. W. Affren Twiner
R. A. Fisher	Denis Williams
[illegible] Gulla	J. Z. Young
I. S. Greenfield	O. L. Zangwill
W. R. Henderson	Editor of the British Medical Journal

EDITORIAL NOTICES

THE EDITORIAL COMMITTEE will welcome original papers. They should be addressed to the *Editor, Journal of Neurology, Neurosurgery, and Psychiatry*, Department of Neurology, Radcliffe Infirmary, Oxford. Papers are accepted on the clear understanding that the subject matter has not been and will not be published in a separate journal.

Papers should deal with original matter and the discussion should be limited to relevant questions. Contributions should be as concise as possible and a short summary of conclusions should accompany each paper. Manuscripts should be typewritten and carefully revised, as alterations in print are costly and, apart from verbal corrections, will be charged to the contributor.

Photographs and photomicrographs should be printed on glossy paper; they should be submitted unmounted, and lettering, when required, should be indicated on tracing paper fixed over the print. Drawings and diagrams should be done boldly in black ink, and any lettering to be done in the editorial office lightly inserted in pencil. Legends should be typed on a separate sheet of paper.

References to papers in the text should be made by inserting the name of author followed by year of publication in parentheses. At the end of the paper, references should be arranged in alphabetical order of author's name. Each reference should give author's name, followed by initials and year of publication in brackets. The name of the Journal in which the article appeared should be given in full and should be abbreviated according to the World List of Scientific Periodicals. The volume number should be given next in Arabic numerals, followed by number of first page of article.

Brown, A. B. (1948) *Amer. Neurol.*, *169*, 427.

Reprints. Twenty-five reprints will be given to the author contributed among the authors. If desired, further reprints may be obtained by application to the Publishing Manager, B.M.A. House, Tavistock Square, but notice must be given when the proof is returned.

Subscription rate, £2 2s. net, per annum, post free. Orders, including orders for single copies, should be sent to the Publishing Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

Applications for advertisement space should be directed to the Advertisement Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 79.

STUDIES IN TRAUMATIC EPILEPSY*

3. VISUAL FITS

BY

W. RITCHIE RUSSELL and C. W. M. WHITTY

From the Department of Neurology, Radcliffe Infirmary, Oxford

The study of epileptic phenomena in wounds of the visual cortex in the widest sense is of special interest, as the clinical features of such cases give relatively precise information regarding the parts of the brain injured.

The cerebral part of the visual mechanism consists of the optic radiation, in which there is a close cell-to-cell pathway between the cells of the lateral geniculate body, and the striate cortex (area 17), which differs from the main sensorimotor area in having no clearly defined projections from the thalamus proper. After this a further wide area of cortex is involved, with visual functions such as spatial orientation, visual recognition and reading, and the visual parts of the body scheme and memory in general. Such areas—the " visual association " or " visuo-psychic " areas—must be regarded as subserving " higher " visual functions in Jackson's sense.

Lesions of the radiations will give sharp-edged visual field defects of hemianopic, quadrantanopic, or segmental outline. Lesions of the striate cortex itself will also cause sharp-edged homonymous defects which may be hemi- or quadrantanopic, but which often have a characteristic scotomatous pattern (Spalding, 1952). Lesions confined to the " higher " visual cortex may sometimes produce permanent changes in aspects of spatial orientation and visual recognition, or such defects as visual inattention, imperception of a stationary as opposed to a moving object, loss of ability to localize an object, or vague blurring of vision in part of a field (though it is possible that some of these may also occur in more peripheral lesions of the visual apparatus); but often they seem to be clinically silent. However, it should be remembered that such " silence " may be in part due to our present ignorance of the functions of these areas. It is thus evident that an exact study of visual fields is of considerable value in localizing the site of wounds, and this is so even when more than one part of the visual pathway is involved. In consequence, the clinical localization in this group of cases is in some ways more accurate than in those involving the sensorimotor cortex.

We must regard the arrival of the neural impulses at the area striata as the first comparatively simple step of a progressively elaborate series of brain events which develop in neighbouring and more remote areas of the brain. This elaboration of what arrives at the striate cortex must be early concerned with the contralateral visual cortex, as well as the adjacent areas 18 and 19, so that the correlation of both sides may form a coordinated whole. Then, the complex mechanisms of memory leading to the ability to recognize, read, place in relation to body and its environment, etc., must be involved. It may be assumed that for an epileptic visual phenomenon (such as flashing lights appearing in one visual field) to occur, some part of the contralateral visual mechanism must be sufficiently active to cause this hallucination. It is, however, largely unknown which parts of the visual pathway must be intact to allow of the development of certain types of visual hallucination. Crude flashing phenomena are generally held to originate near the visual cortex, but this is a loose anatomical phrase and the matter should, if possible, be investigated more precisely. The appearance of hallucinations in blind half-fields is of special interest, because some part of the visual mechanism for that field must be preserved for visual phenomena to occur therein. It may be supposed either that the damaged area, although not able to function " normally ", has yet enough cells left to fire epileptically, or that areas separate from, and at a higher level than, the damaged area themselves fire spontaneously to produce the hallucination. The development of homonymous hemianopia as an epileptic phenomenon is also worth careful consideration, and suggests that some groups of cells have inhibitory or suppressor functions, and, since these cases have intact fields

*Parts 1 and 2 appeared on pages 93, vol. 15 (1952) and 73, vol. 16 (1953) respectively.

between attacks, they would seem to be in areas other than those concerned primarily with positive visual reception. Finally, the complex hallucinations with recognizable objects, people, places, or events give a glimpse into one of the highest cerebral mechanisms. Such hallucinations at times appear similar to visual memory and are referred to by the subjects experiencing them as " memories ". Presumably all recognition must involve a memory process ; however, these complex phenomena, which may form a static picture but often have a temporal element, in that events occur during hallucinated scenes while they last, would seem particularly to involve the highly integrated mechanisms that are usually referred to as " memory ".

Reference to cortical function as a separate entity involves an over-simplification of a complex mechanism, for all cortical activity leads to a multitude of associations along many pathways, and in this connexion the cortico-thalamic connexions are no doubt specially important. Thus it is of interest to consider not only which part of the visual system is discharging, but also whether the discharging focus is in any way isolated from lower levels of the visual mechanism, or whether the pathways to the higher visual centres are intact or damaged, for functional damage to higher cortical mechanisms may presumably be caused by injury to white matter conveying cortical association tracts or thalamic connexions. The connexions of the occipital and parieto-occipital lobe with the pulvinar are obviously of great importance, and in many of our cases these connexions must be damaged. Furthermore, we must bear in mind the possibility that para-calcarine cells are just as likely to originate visual hallucinations as are those of area 17 itself.

In this study, therefore, these problems and possibilities should be kept in mind, and an attempt made to search for anatomical implications and correlations.

Case Material

This paper reviews 60 cases of brain wounds having epilepsy with a visual aura, and Table II gives a summary of the clinical details, including tracings of skull radiographs and visual field charts where available, for all cases. It can be seen that a wide variety of visual phenomena occur, from the simplest unformed visual hallucination to such complex effects as remembered scenes or agnosia for visual objects.

Evidence as to the exact site of a lesion is largely inferential and may be inaccurate. Bearing this in mind, we have nevertheless attempted to group the cases into three main anatomical divisions : (1) Those with injury chiefly to the calcarine cortex, based on the type of field defect—a homonymous congruous scotomatous defect or defects—combined with the site of wound and direction of missile ; (2) those with definite radiation lesions as indicated by a permanent hemianopia, quadrantanopia, or sharp segmental field defect, and the site and direction of the wounds ; (3) those with lesions of the " higher " visual cortex—that is the parietal or occipital areas, but forward of the calcarine cortex itself, based on the site and direction of the wound together with an early transient field defect or some permanent change such as visual inattention, disorientation, agnosia, etc., but without the interruption of optic radiations which produces a permanent dense field defect. Such a grouping is not necessarily exclusive, since wounds of the radiations, for instance, will in many, if not the majority of, cases involve also "higher" visual cortex and some of the calcarine wounds may also involve other visual cortex or radiations. Nevertheless, it is of some practical value in attempting to correlate the site of wound and type of fit.

Group I : Wounds of the Calcarine Region

Nine cases have been placed in this group, but there are remarkably few small wounds of the calcarine cortex with focal visual fits, and in still fewer of these cases is the field defect confined to the dense paracentral scotoma characteristic of localized posterior calcarine wounds. Cases 1 and 2 are perhaps examples of this. Case 4 had some destruction of one occipital lobe as well as of the calcarine cortex. Case 9 had widespread damage to the left hemisphere as well as a lesion of the right calcarine area, while Cases 5, 6, and 8 almost certainly had additional radiation lesions. Case 3 had a small wound near the calcarine cortex though its exact anatomy cannot be determined. Case 5 is one of almost complete cortical blindness, and sparks of light appear as an epileptic aura. Presumably these discharging cells are situated in the upper occipital region at a physiologically higher level than the calcarine cortex.

In this group the visual hallucinations tend to be continuous unformed visual phenomena, usually with an element of movement in them : weaving patterns, zigzag lights, showers of sparks or coloured clouds are described, rather than interrupted flashes of light. The hallucinations appeared also in the segments of field loss due to damage to the calcarine cortex, and this supports the view that these crude visual phenomena originate at a higher level than area 17. In one case (No. 6), in which a missile was removed from the right calcarine cortex but

with additional more anterior cortical damage, there was a continuous sensation of coloured lights in the blind part of the field. Although varying in intensity, this had been present continuously for nine years since wounding. In some ways this is reminiscent of the continuous dyaesthesiae or pain sometimes seen in thalamic lesions. However, as has been pointed out, none of these cases had very sharply localized wounds and it may be assumed that cerebral damage extended beyond area 17.

In order to provide a background of the general incidence of epilepsy in these cases, Table I analyses the type of fit occurring in an arbitrary 225 cases which fall into the three anatomical groups we are considering.

In Group I there is a lower incidence of epilepsy in the unilateral wounds of the occipital pole than perhaps in any other area of the brain (six out of 24), but when fits occur they usually (four of the six) have a visual component.

The bilateral wounds of the occipital lobes also have a relatively low (11 out of 36) total incidence of fits and a strikingly low incidence of visual fits, which appeared only in one case.

There is therefore little to suggest that patients with small wounds of the calcarine cortex are specially liable to visual fits ; indeed fits of any sort seem less likely to occur than with wounds in most other cortical sites.

Group II : Radiation Lesions

Wounds of the optic radiations will always involve parts of the cortex also. Thus they may injure the upper part of the occipital lobe and nearby parieto-occipital and posterior parietal cortex and spread down to involve radiations, or they may involve the temporal cortex more anteriorly and penetrate to sever the anterior part of the radiations. The pattern of visual fits that develops may therefore be affected both by the cortical wound and the radiation lesion. Of the 21 cases in this group, there are relatively few with wounds of the anterior part of the optic radiation and visual fits. The most clear cut are those in which chiefly the lower half of the optic radiation in the temporal lobe is damaged. There are only two examples in the series (Cases 22 and 23). In the first, the visual fit took the form of a negative phenomenon—hemianopia followed by flashing lights in the extinguished field : in the second, elaborate, formed visual hallucinations occurred. However, the total incidence of epilepsy in such wounds is by no means low, for in a group of 42 cases with this anterior type of radiation lesion no fewer than 22 had fits of some sort (Table I).

In eight of the cases with hemianopia or lower quadrant defects there was also some permanent hemiparesis, while in 13 (including the two mentioned above) there was no permanent motor loss. Wounds in the former group were in general probably rather more anterior than in the latter, Nos. 22 and 23 being exceptions, but no obvious differences emerge in the pattern of visual fits which occur in the two groups. In all these cases the occipital poles were intact and the radiation lesions must have produced isolation of at least a part of the calcarine cortex from afferent visual impulses. Isolated neurons are known to show rhythmic spontaneous firing (Brazier, 1951), and " deafferentation " of an area of cortex might therefore be expected to influence both the pattern and frequency of epileptic fits firing from it. In Table I, of a total of 79 cases with radiation lesions and partially isolated calcarine cortex, 45 had fits of some sort, but only 12 of these had a visual aura. Such isolation does not therefore seem important in producing visual fits. These figures also make it unlikely that an irritative lesion of the radiation alone has epileptic potentialities. As Table I shows, when radiations are involved more posteriorly and the higher visual cortex is therefore probably also injured, the incidence of epilepsy rises and a higher proportion of those with an aura have a visual one.

When we consider the pattern of visual seizures in these radiation lesions, two broad groups can be recognized. First, complex phenomena such as formed visual hallucinations, distortions, and loss or blurring of a half-field, and secondly, crude phenomena such as interrupted flickering or flashing lights. Only one case showed the continuous moving lights commonly seen in calcarine wounds. As will be shown later, complex hallucinations and negative phenomena tended to occur in cases where

TABLE I

TYPE OF FIT IN THREE MAIN GROUPS OF CASES

	Total	No Fits	Grand Mal with No Aura	With Visual Aura	With Non-visual Aura	Total Fits
Group I unilateral ..	24	18	1	4	1	6
(Calcarine) bilateral..	36	25	6	1	4	11
Group II anterior radiations giving field defects	42	20	11	1	10	22
Group II more posterior wounds with field defects	37	14	3	11	9	23
Group III higher visual cortex without permanent field defect..	86	40	15	13	18	46
Totals	225	117	36	30	42	108

the higher visual cortex was damaged without there being any permanent dense field defect. It may therefore be supposed that such phenomena in this present group represent ictal firing from the cortex damaged at the wounds of entry and are not influenced primarily by the injury to the radiations. Formed visions or distortions occurred in five, and negative effects in six, of these 21 cases; in one continuous moving lights, and in one a ball of stationary light followed the negative effects. Interrupted flashes occurred in 10, and in a further one such flashes also occurred together with the extinction of part of a field as a negative effect. Interrupted light is thus a common phenomenon when visual fits do occur in this group. It may represent one aspect of the spontaneous firing of isolated calcarine cortex, though the following case makes this unlikely to be the whole explanation.

Case 17.—Fits would begin with the sudden flashing on and off at a rate of about two per sec. of a bright yellow light in the left (blind) visual field. This continued for a few seconds and the patient would lose consciousness and have a generalized grand mal attack.

Following surgical excision of a part of a right temporo-occipital brain scar and of an area at its anterior margin where a spike focus was defined by electrocorticography, the fits became less frequent and changed in character. Usually no aura of any sort occurred and the patient would suffer the abrupt onset of a grand mal convulsion. Rarely a brief aura, " a feeling of unsteadiness", would precede the convulsion.

In this case the removal of cortex well away from the occipital pole abolished the flashing. This cannot have affected whatever spontaneous activity occurred in the calcarine area. It may be argued that the hallucinations of flashing lights resulted from the arrival of calcarine discharge at the more anterior cortex, which was removed. However, the excision extended deeply and would have interrupted connexions between the pulvinar and peristriate cortex, and the consequent interruption of the thalamic contribution to cortical activity may just as well have been responsible for the result. The case serves to illustrate once more the complexity of cortical function.

That a high proportion of non-visual fits occurs with wounds in the anterior occipital or posterior parietal and temporal areas causing radiation lesions is understandable if we consider that these fits represent a discharge from cortex at the site of entry which may have only slight associations with visual function.

This group provides some interesting examples of complex hallucinations, and although they must be grouped anatomically as radiation lesions some of them will be discussed more fully in the section dealing with cases of " higher " visual cortex lesions without permanent field defects.

Group III. Higher Visual Cortex Lesions

There are 30 cases which fall into this category, several with more than one kind of visual fit. Their most frequent and perhaps best defined clinical manifestations are the negative ones—complete blindness, or hemianopia, or sudden blurring in a half-field. This occurred as the onset to an attack in 16 cases. Sudden bilateral blindness, or hemianopia, or a gradual field defect spreading to involve one half-field or the whole of vision are all exemplified here. In one case the defect was a momentary affair like a shadow crossing one half-field. In addition, blurring of vision so that objects could not be seen clearly occurred both in one half-field and for complete vision. In four cases after the extinction of part of a field, interrupted flashes of light then appeared in the blind field, a sequence of events noted by Penfield and Jasper (1954) following electrical stimulation of certain peristriate points, and in two cases a continuous stationary light was experienced. It is noteworthy that no instances of formed hallucinations were recorded following a negative visual phenomenon.

These are posterior and often high parietal wounds and usually well above the optic radiation. There may be some sensory or motor loss but there is no dense visual field defect. Some of the negative phenomena appear to be examples of true inhibition and may be compared with the inhibition of motor activity as reported in our previous study of focal motor fits (Russell and Whitty, 1953). The tendency for a hemianopic or complete field distribution rather than any scotomatous or segmental type of defect to occur is striking.

In 18 cases distortions of vision occurred. Objects seemed far away, in the wrong place, unfamiliar, and distorted in shape, or actually appeared to be moving (both receding and moving to one side were described) when stationary. In one (Case 50) there was a definite spatial disorientation sufficient to make it difficult to move around in familiar surroundings. One other patient (Case No. 34) had a visual agnosia during his attacks. This patient had some permanent difficulty in localizing objects presented in the left half-field, and objects appeared less distinct on this side. However, there was no complete field defect of any sort. Nor was there any permanent difficulty in recognizing objects, though there was possibly a slight dyslexia and a definite dyscalculia. His attacks started with the abrupt onset of a left hemianopia, which was followed rapidly by a dysphasia, receptive and

expressive. Sometimes at this stage he would be unable to recognize objects though he could see them. This occurred only in some attacks, and was quite distinct from his dysphasia which constantly accompanied all attacks.

The case is of special interest because it illustrates the problem of what aspects of visual function must be regarded as a whole-field phenomenon. Agnosias are generally considered to be such, though recently Bay (1953) has suggested that they may, in fact, sometimes be only perceptual difficulties which may be limited to a part of the visual field, though producing a general effect on visual appreciation. In the case here described certain visual defects were permanently present in one half-field, and a complete hemianopia occurred during attacks, sometimes with and sometimes without agnosia. The hemianopia cannot therefore be a factor in the agnosia : and the case seems to support the view that agnosia is a defect of total vision fired from one hemisphere.

Attacks in which distortion of vision, apparent displacement of visual objects, and spatial disorientation occur, examples of all of which are recorded here, also illustrate this problem, since in all of them a localized field abnormality might be the basis of what the patient describes as a generalized effect.

In five cases aphasia occurred as part of an attack with visual element. In one case (Case 58) it initiated the attack and was followed by visual phenomena—disappearance of objects and a bright light. In the other four (Cases 34, 42, 50, and 57) visual phenomena appeared before the aphasia. Of these, one (Case 34, already detailed) had an occasional associated visual agnosia in his attacks and another (Case 50) occasional spatial disorientation. This association with aphasia is worth comment, for, unlike the focal attacks occurring in wounds of the sensorimotor cortex (Russell and Whitty, 1953), the present cases show little tendency for the content of fits to spread from visual to non-visual phenomena or vice versa. Thus, of the whole series, in only nine cases did an aura start as a visual one and spread to the non-visual sphere. In four cases the spread was to aphasia, in four to positive motor phenomena, and in one to sensory. Seven cases showed a spread from a non-visual to a visual aura, and of these one started as aphasia, four as a focal motor phenomenon, and two as a non-visual sensory one. So far as a change of a visual aura itself is concerned, it is interesting that 11 instances showed a progress from negative to positive visual phenomena, while only one showed a change from positive to negative and only two a change from one form of positive to another.

In two cases in this group interrupted flashes of light occurred as the whole content of a focal fit, in addition to the four cases where this was secondary to the extinction of part of a field. In one case also continuous moving lights, of the kind more commonly seen in calcarine lesions, were reported.

Many unusual varieties of focal fit may originate in the posterior parietal lobe. Thus in Case 54 the eyes were forced upwards, and in Case 40 adversive movements of the head and eyes occurred from small wounds in this region.

But perhaps the most interesting of any are those in which visual aspects of the body image and memory mechanisms appear to be involved. Two cases of the former and five of the latter are recorded in this group ; however, as further examples of both these also appeared in the group of radiation lesions we consider them together in the present section. The anatomical group to which each case is assigned may be seen from Table II.

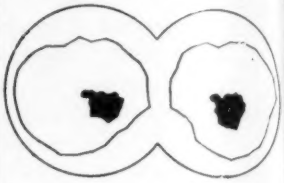
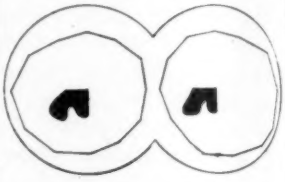
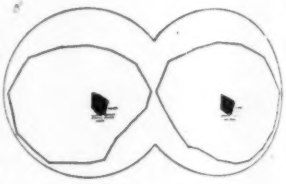
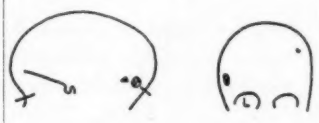
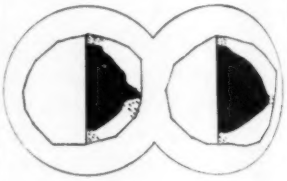
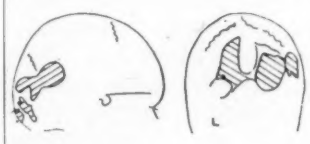
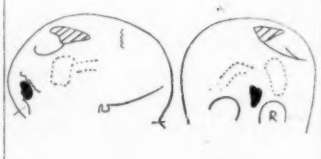
Before mentioning them in more detail, we may see from Table I that the general incidence of epilepsy in 86 cases of Group III is high (46 out of 86). However, of the 31 of these with focal fits or aura, only 13 were visual and 18 non-visual. This is probably a reflexion of the fact that some of these wounds impinge on the more posterior parts of the main sensorimotor cortex.

In four of our present cases the visual aspect of the body image was involved in their attacks. In two there was a localized involvement, and in two the upset was more general.

Case 40.—This patient had four types of attack : grand mal without warning ; right adversive attacks involving the hand and eyes which led to momentary loss of consciousness ; and a sudden shadow moving across the right half visual field, " like a cat running across " without loss of consciousness. In addition there were episodes in which his right hand would suddenly seem to be raised up above his head, and he would look up towards it and seem to see it momentarily, and on occasion had asked his wife to pull it down. The attacks lasted for less than 30 seconds, and ended abruptly ; there was some confusion during them, but if his attention was directed towards his hand in its real position he would admit to seeing it there.

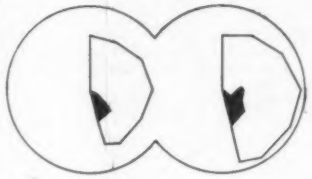
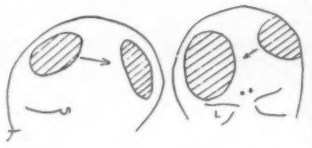
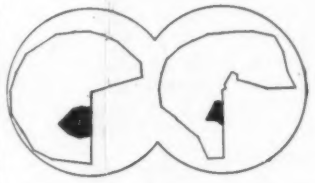
Case 25.—This patient's epilepsy was of sudden attacks in which his left hand looked queer and out of place ; it did not appear to be in the place he felt it. He felt the limb did not belong to him, and would waggle his fingers and watch them moving to assure himself that what he was looking at was his own limb. This sensation lasted for a few seconds only, after which he lost consciousness and had a generalized grand mal convulsion. On other occasions he had the aura only, without any grand mal attack.

TABLE II: SUMMARY OF CLINICAL DETAILS

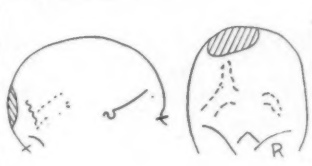
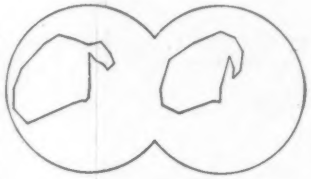
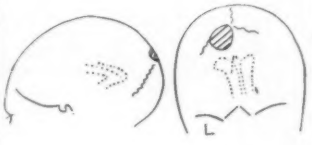
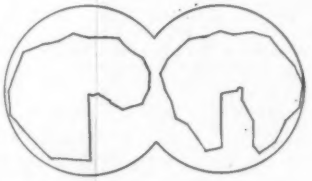
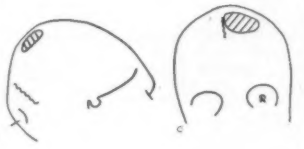
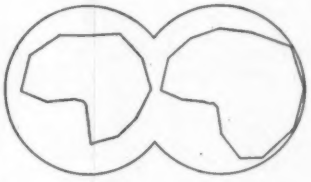
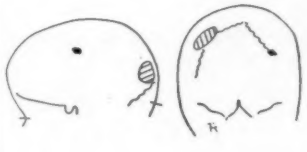
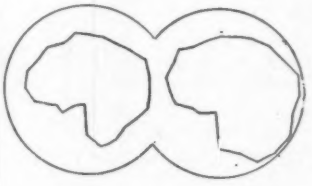
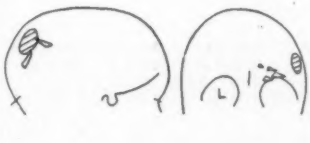
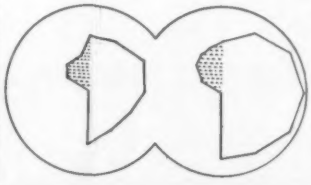
Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
	GROUP 1.—*Calcarine Lesions*		
1 (158). Midline. Handedness not known. No sensory or motor loss	1. Zigzag ring of light in front→gets bigger till ring reaches limit of sight range→clears→headache 2. Head starts to spin→loss of consciousness		
2 (373, 1st series). R. side. No sensorimotor loss	1. Flickering bright colours appear in L. field (especially lower blind L. field)→pictures seem to appear in centre of colours flashing past horizontally (unable to recognize them)→suddenly stops 2. 1→loss of consciousness		
3 (365). L. side—2 wounds. No sensorimotor loss	1. Cry→general convulsion 2. Live wires dancing in front of eyes for a few minutes		
4 (895). L. side. No sensorimotor defect	1. Things seem more blurred, then white weaving pattern appears in defective field		
5 (550). R.→L. Sensory loss L. limbs, with some paresis. Cortical blindness	1. Spasm of L. arm and leg 2. Thousands of sparks of light whirling about→head spinning→L. arm and leg spasms→loss of consciousness		
6 (459) R. side. L. hemiparesis with some sensory loss	1. Spasm of L. arm and leg→loss of consciousness 2. Sudden feeling of great anxiety for 5 min. 3. Continual flickering lights and colours in blind part of visual field—still present after 9 years		
7 (491). R. side. No sensorimotor loss	1. Like a windmill going round for 5 min. in L. (hemianopic) field		

continued

TABLE II *continued*

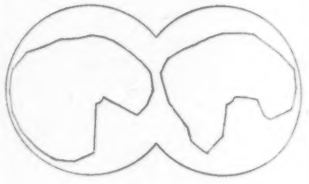
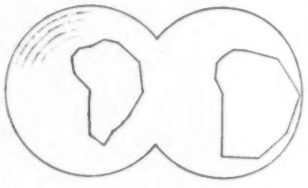
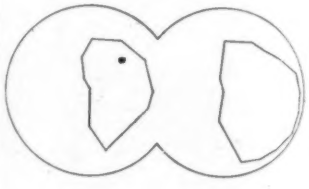
Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
8 (550). R. side. Early blindness, and weakness L. leg. Later : no sensorimotor signs	1. Suddenly the blind half-field is filled with hundreds of tiny sparks of coloured light —red, blue, and green, moving downwards like snowflakes→loses consciousness→ grand mal 2. Coloured fog appears in blind field—several overlapping colours float about→grand mal 3. Either 1 or 2 without loss of consciousness or convulsion		
9 (817). R.→L. L. hemiplegia, severe sensory loss	1. Continuous flickering lights, usually white, sometimes coloured, L.→R. passing into the blind field and lasting for 20 min. 2. Twitching L. forefinger and thumb 3. Visual loss→general convulsion		

GROUP II.—*Radiation Lesions with no Sensorimotor Loss*

10 (667). L. side. Early dysphasia and visual distortion. No sensorimotor loss	Sees people he knows telling him to get up →grand mal (Described more fully in text)		
11 (456). L. side. No sensorimotor disorder. Some spatial difficulties	1. Head and eyes to R. General convulsion 2. R. field blacked out→bright white or coloured lights moving up and down in R. blacked-out field affects whole R. field, including defective segment →general convulsion after 5–10 min. Severe headache on recovery 3. As above, but after coloured lights hallucination of remembered war scenes→ loss of consciousness (Described more fully in text)		
12 (362). R. side. L.-handed. No sensorimotor loss. Defective localization and colour sense in upper L. field	1. Sudden flashing red light in L. field 2. As in 1 →loss of consciousness		
13 (654). R. side. No sensorimotor loss	Flashing light in L. field →grand mal		
14 (755). R. side. L.-handed. No sensorimotor disturbance. Attention and orientation defects in partially preserved L. upper field. Topographical difficulties, also with judging speeds and distances	1. Flashing lights in hemianopic field, then to R. and obscures vision (lasts for 10 min.) 2. Attacks of loss of consciousness—no aura		

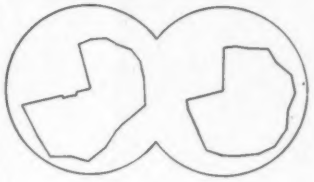
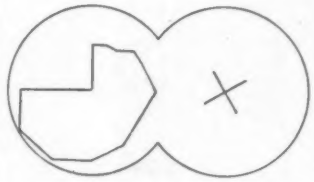
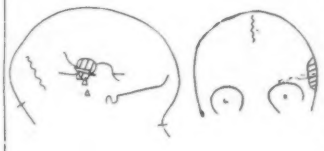
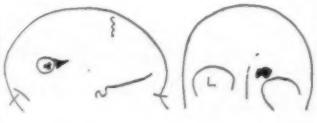
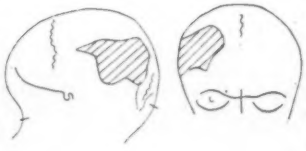
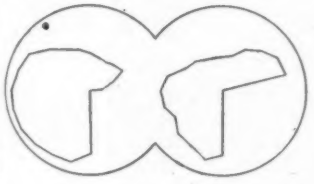
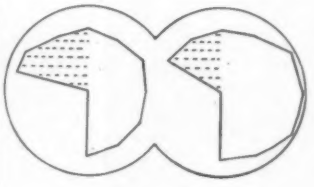
continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
15 (132). L. → R. No sensorimotor loss. Some dysphasia, and memory poor	1. Cry → general convulsion 2. Coloured lights flashing on and off in R. field → noise in head → loss of consciousness and convulsion		
16 (179). L. side. Occasional slight dysphasia	1. Vision blurs 3–4 sec. → general fit 2. Above aura only		
17 (R.I. 167943). R. side. No sensorimotor loss	Sudden flashing on and off of a bright yellow light in the left (blind) field. Loss of consciousness → grand mal (Described more fully in text)		
18 (529). L. side. No sensorimotor loss. Dysphasia	1. Spasm R. hand → general convulsion 2. Short periods of flashing lights in blind field		
19 (562). R. side. No sensorimotor disorder	1. A hot smell, and things go blurred 2. L. arm goes dead 3. Distorted hearing → loss of consciousness		
20 (211). L. side. No sensorimotor loss. Dysphasia	Vision blurs → flashes of light for ½ hour, seen in lower field R. and L.		
21 (883). R. side—developed abscess. Slight sensory loss L. hand	1. Sees a cabbage in L. lower field → general fit 2. Sees a mountain with snow on top which he climbs. When he reaches the top → general fit. May be followed by weakness of L. limbs		

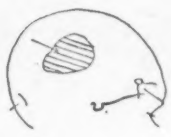
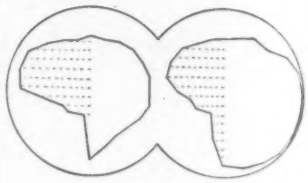
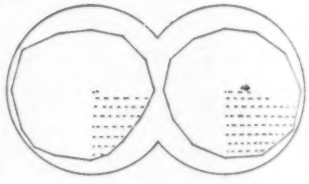
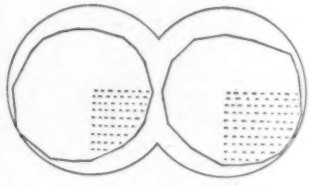
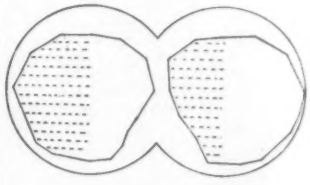
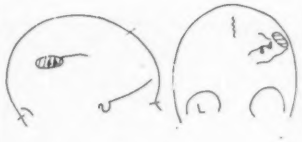
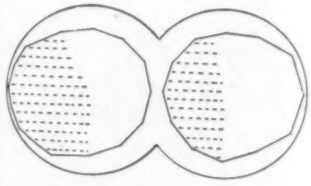
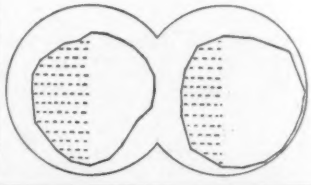
continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
22 (547). R. side. No sensorimotor loss	1. Sudden giddiness, with loss of sight, and coloured lights and circles in L. field 2. General convulsion		
23 (1030). R. side. No sensorimotor signs. R. eye destroyed	1. Major convulsion—no aura 2. Multiple hallucinations of himself (head and shoulders to waist) in miniature in L. field (Described more fully in text)		
GROUP II.—*Radiation Lesions with Sensorimotor Loss*			
24 (534). R. side. Slight L. hemiplegia with sensory loss. Spatial difficulty and body image upset	1. Shock in L. hand, tonic L. arm →loss of vision with a "familiar" hallucination which he cannot remember. Lasts for 1–2 min. L. foot weaker after 2. 1 →Loss of consciousness (Described more fully in text)		
25 (266). R. side. Slight L. hemiparesis with sensory loss. Topographical difficulty	1. Phantom movement of L. hand, partly visual 2. 1 →general convulsion (Described more fully in text)		
26 (23). L. side. Slight R. hemiparesis with sensory loss and dysphasia	1. Twitching R. hand →general convulsion 2. Loss of feeling R. hand and loss of vision		
27 (468). R. side. Severe L. hemiplegia, with sensory loss. Blurring and inattention L. upper field lower quadrantanopia	Head to L. →flashes of yellow light in L. lower field →loss of consciousness, but lies still		
28 (781). R. side. Severe L. hemiplegia with sensory loss. Delayed but excessive reaction to pinprick	Flashing light to L. →general convulsion		

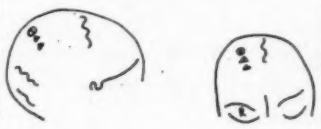
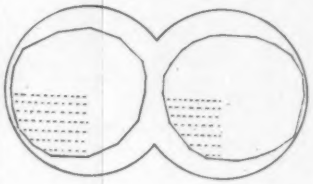
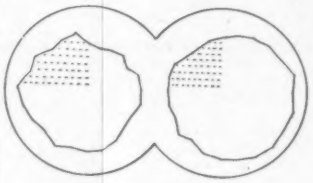
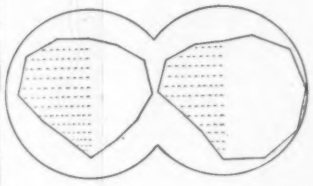
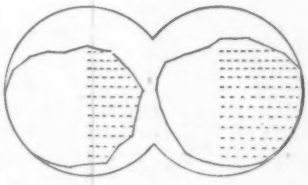
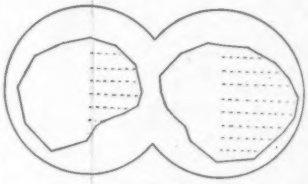
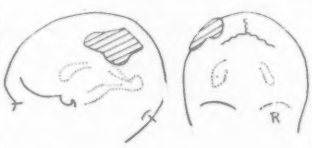
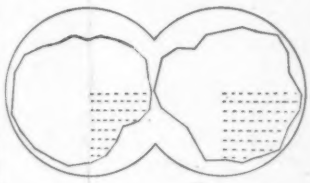
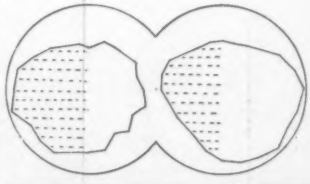
continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
29 (899). R. side. L. spastic hemiplegia with sensory loss	1. Flashing light to L. →clonic movements L. arm and leg 2. 1 →grand mal		
30 (196). R. side. Slight L. hemiparesis with sensory loss. Blurring and inattention in L. upper quadrant	1. Flashing white light in L. field 2. Objects quiver →loss of consciousness (only on standing up suddenly)		
GROUP III.—*Higher Visual Cortex Lesions with some Permanent Visual Field Change*			
31 (931). L. side. Slight weakness R. arm. Early R. lower quandrantanopia. Slight disorientation R. lower field later	R. hemianopia →grand mal		
32 (721). L. side. Slight weakness R. leg. Slight dysgraphia and confusion of laterality. Early R. homonymous hemianopia. Later, fault in localizing objects in R. lower field	1. Little round things in front of eyes which get bigger and bigger till can't see. Gradually subside in 15–20 min. 2. Suddenly can't see straight ahead, but has to look out of corner of eye		
33. (4122). R. side. Moderate sensorimotor weakness of L. leg. Disorientation in L. half-fields	1. Twitching of lips →blurring of vision like a shadow over L. field →general convulsion 2. L. hemianopia for ½ hour 3. Numbness of L. arm for 5 min.		
34 (739). R. side. No sensorimotor loss. Dyscalculia. Slight blurring and spatial difficulty in L. field, more lower than upper	Loss of vision in L. field for ½ hour, with mental confusion and aphasia. Sometimes visual agnosia		
35 (673). R. side. Slight sensory loss L. arm. L. upper half-field blurred, more marked lower quadrant	Everything starts to move →grand mal		

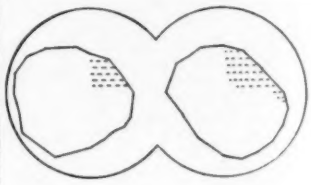
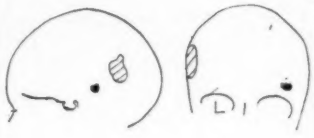
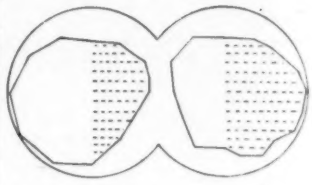
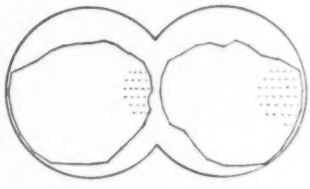
continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
36 (328). R. side. Early L. hemiparesis, with sensory loss and hemianopia. Now only blurring in L. lower quadrant	1. Numbness L. arm → L. leg → clonic movements arm and leg 2. Numbness L. arm, arm feels strange and "will not obey commands" 3. Suddenly everything looks far away and out of focus		
37 (584). R. side. Handedness not known. Early L. hemianopia. Later topographical disorientation and upper L. quadrant blurring	1. Lot of coloured lights and flashes 2. 1 → grand mal		
38 (898). L. → R. Weakness and sensory loss in R. leg. Vision blurred in L. field, with defective localization, especially in lower quadrant	1. Blue light flashes in L. field → general convulsion 2. General convulsion with no aura		
39 (293). L. side. No sensorimotor loss. Early R. central scotoma. Later, R. half-fields blurred and objects tend to disappear when not moving	Zigzag lights in R. half-field for 20 min. → pale and confused		
40 (71). L. side. Slight cortical sensory loss. Early R. hemianopia, later localization defective in R. field	1. General convulsion 2. Phantom movement R. hand 3. Head and eyes to R. → momentary impairment of consciousness 4. (Early only) sudden shadow across R. field (Described more fully in text)		
41 (599). L. side. Slight sensory disorder R. hand. Occasional agnosia R. arm. Visual imagery impaired. Slight dysphasia. Some blurring in R. lower quadrant	1. Rotation to R. 2. Autoscopic hallucination with feeling of detachment (Described more fully in text)		
42 (2366). R. side. Sensory loss L. side. Defect lower L. field to stationary objects, also attention defect and failure to localize in whole L. field	1. Hot → thoughts race → dreams he is back in Khartoum → sees and recognizes people → clonic movement of face 2. Jerking of L. face, aphasic → rotation to L. → reverse → loss of consciousness (Described more fully in text)		

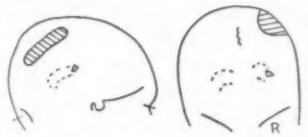
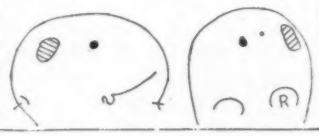
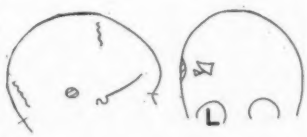
continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
43 (554). L. side. No sensorimotor loss. Slight dysphasia—frontal lobe type of behaviour. L. upper quadrant visual blurring	1. Hallucinations of remembered scenes in R. half-field 2. Sudden aphasia and word deafness 3. Sudden compulsion to look to R. 4. General convulsion		
44 (401). L. side. No sensorimotor loss. Dysphasia and impaired topographical sense. Occasional perseveration of vision soon after wound; saw things after they had gone away. Blurring and attention defect in R. half-field	1. Hallucination of remembered scene on his R. (black and white) → general convulsion 2. Dazed → general convulsion (Described more fully in text)		
45 (865). L. side. No sensorimotor disorder. Slight blurring of R. half-fields	1. R. hemianopia, then flashing red light from R. spreading to centre and quickening to about one a second, continuing for 30 min. Both clear quite suddenly and are followed by L. occipital headache 2. Hallucinations of remembered scenes of experiences after wounding in the R. half-fields → dazed and aphasic → weakness R. arm (Described more fully in text)		
GROUP III.—*Higher Cortex Lesions with Visual Field Defect but No Persistent Field Change*			
46 (94). L. side, parasagittal. L. handed. No sensorimotor loss	1. Blurring of sight → grand mal 2. Grand mal		Early R. lower quadrant defect; fields full now
47 (103). L. side. Transverse occipital wound at calcarine level. *Early:* transient blindness, then R. hemianopia which cleared; L. tinnitus, also dysgraphia and confusion of laterality	1. Suddenly can't see to R. side, then red spot appears to R. L. tinnitus increases → loss of consciousness 2. General convulsion—no aura		Blurring in R. upper quadrantic field, attention defect in R. field
48 (751). R. side. Severe L. hemiplegia and loss of sensation	1. Face twitches → feels hot above eyes 2. Feels faint → vision goes black → flashing light in L. upper field for a few seconds followed by headache for an hour 3. Twitching L. arm and L. leg → hot feeling		Fields full, but early L. hemianopia
49 (127). L. side. No sensorimotor loss. Slight dyslexia	R. hemianopia, lasting for up to 2 days		Early hemianopia cleared
50 (702). L. side. L. handed. Moderate R. hemiplegia, with aphasia	1. Mind hazy → things moving to R. → unable to speak → R. field blurred → R. hand dorsiflexing and elbow flexing 2. Grand mal 3. Sudden hemianopia for ½ hour (during one he lost himself in familiar surroundings)		No field defect now, but early R. hemianopia

continued

TABLE II—*continued*

Clinical Features	Type of Fit	Skull Radiograph	Visual Fields
51 (2782). L. side. Slight weakness R. hand	1. Jerking of R. arm and leg → weak arm 2. Dizziness → blackness of vision		Early R. hemianopia, momentary blindness. No permanent field defect
52 (881). Central. Severe paralysis both legs and R. arm, with sensory loss and some dysphasia	1. Turning head to R. → loss of consciousness 2. R. hemianopia with flashing lights in R. field		Fields full, but early R. hemianopia
53 (52). R. side. Horizontal high parietal scalp wound. Slight sensori-motor loss in L. arm	1. Hemianopia, then flashes of blue light to L. for 5 min. 2. 1 for 2 sec. → major fit		Early L. field defect ; fields now full
54 (76). R. side. L. hemiplegia, with sensory loss	1. Eyes turn up → " loses sight " → calls out " I can't see, put me somewhere " → major fit 2. Everything seems to move → face twitches → loss of consciousness		No field defect, but early L. hemianopia
55 (214). R. side. Severe cortical sensory loss, slight weakness on L.	Objects appear misplaced → head to L. → grand mal		Fields full, but early L. hemianopia
56 (602). R. side. Handedness not known. Cortical sensory loss L. arm and leg	1. Early visions of platoon commander in blind field 2. Spatial disorientation → pain in L. hand and leg → twitching L. face (Described more fully in text)		Early L. hemianopia—fields now full
GROUP III.—*Higher Cortex Lesions with Fields Always Full*			
57 (280). L. side. No sensori-motor defect	1. Sight goes → aphasic → fall → general fit 2. General fit ; no aura 3. Eyes blur and empty feeling inside		Fields full
58 (102). L. side. No sensori-motor loss. Dysphasia	1. Scream and half-turn → fall with convulsion 2. Aphasia → objects seem to disappear and bright light in front of eyes		Fields full
59 (894). R. side. No C.N.S. signs	1. Objects suddenly appear to recede → loss of consciousness 2. Rarely, grand mal attack		Fields full
60 (391). R. side. Slight weakness of L. leg	1. Everything looks distorted → fall (? unconscious) 2. Sudden fall and unable to move for 3–5 min.		Fields full

All cases are right-handed unless otherwise stated.

In the first case phantom movement of one limb occurred and the attack involved mainly kinaesthetic sense though there was a visual element to it in that he would at times look up and seem to see the limb in its phantom position. In the second the feeling was more ill-defined ; the limb looked queer and was in the wrong position, though the visual element to the dysfunction was more definite. These may be compared with localized or lateralized visual field phenomena such as hemianopia, etc. The following two represent a more intrinsic upset of the body scheme.

Case 41.—The patient's attacks were of two sorts. In one there was a sudden intense feeling of rotation always to the right. If walking, he would be forced to veer to the right in a circle. This would last for a few seconds only and end abruptly. In the second and less frequent one he would have a sudden feeling of being detached from his body, so that he was observing it as if looking at someone else. There was a definite visual quality about the attacks, which he described as, " I see myself as separate and watch myself from outside and slightly above me". On one occasion this had led on to loss of consciousness and falling.

Case 23.—This patient had a variety of epileptic phenomena. Early after wounding he had sudden grand mal attacks without any aura. Later, attacks occurred in which objects he was looking at would suddenly fade out and be replaced by a black or grey spot which would spread to cause a complete left hemianopia. This would sometimes lead on to a grand mal attack. In others, the left half-field was suddenly filled with coloured balls of light, and as he looked at them they changed to multiple tiny figures of men. On later occasions he saw these figures and recognized them as multiple images of himself, tiny replicas which seemed to move towards him and then recede again : they were head and shoulders only, and if he moved his arms the figures seemed to move theirs in a similar way. For a limited period of several days together he also had attacks of a sudden black spot obscuring his vision, but, instead of remaining a negative phenomenon, the area was suddenly occupied by a normal life-size picture of a man's head and shoulders : as he looked, " it suddenly dawned on me it was myself". It was a mirror image, and again could be made to imitate movements he himself made. On occasion all of these hallucinations had been the aura to grand mal attacks. (This case has already been mentioned in a study of autoscopy by Dewhurst and Pearson, 1955.)

In both these cases the mechanism for central integration of the body image itself seems to be involved, but in two different ways. In the first, Case 41, he is watching the visual impression of his own body image from without, as if the visual (exteroceptive) and postural and kinaesthetic (enteroceptive) elements of the scheme had become separated. In the second (Case 23) we see a gradual build-up of a fully formed " autoscopic hallucination " from what at first seems to have been a simple, almost unformed, visual hallucination. In the one case the discharge seems to occur directly within the areas concerned with formulating the visual body image. In the second, a discharge originally from some relatively primitive visual area is secondarily elaborated by other parts of the cortex at first into figures and finally into figures of the self. Such a process may well be important in the formation of one type of autoscopy, and it would be of interest to know whether it represents a gradual spread of some epileptic discharge in recurring attacks so that more widespread areas of cortex are involved, or whether the discharge remains confined to its original circuits, but the normal cortex around it gradually reacts to the discharge in such a way as to produce the feeling of autoscopy.

Finally, in the formed visual hallucinations of remembered scenes, the problem of both whole-field organization and the possible " elaboration " of the primary hallucination occurs.

In nine cases, five stated that their hallucinations were in only one half of the visual field, always that half which had some loss of function either early after wounding or permanently. All were able to describe the hallucinations in detail. Of these cases, Nos. 43 and 45 have already been reported as examples of epileptic hallucinations of remembered scenes (Robinson and Watt, 1947) and No. 44 has been referred to in connexion with loss of " number form " following brain wounds (Spalding and Zangwill, 1950).

Case 45.—This patient, in addition to attacks of intermittent, red, flashing lights in the right half-field, would suddenly see in this field pictures of his experiences immediately after wounding. He would see stretcher bearers walking past and then the figures of nurses whom he would recognize. The figures were smaller than normal and seemed flat and uncoloured rather like a cinema film. They appeared in addition to real objects seen in the left half-field.

Case 44.—In his first fit only, there was a clear-cut visual aura at the onset. Suddenly in the right half-field a scene appeared in black and white. It was an outdoor scene with fields and trees and it seemed like a part of the landscape near his home, though he could not place it precisely. There was some vague movement of objects—a swaying of trees, etc.—in the hallucination, but just as this began he lost consciousness and fell. A generalized fit followed, in which there was some stiffening with tongue biting, but no clonic movements were recorded.

Case 56.—His visual attacks consisted of sudden spatial disorientation followed by pain in the hand and

leg and then twitching of the left face with some clouding of consciousness. In attacks early after wounding when he still had a partial left hemianopia, the blind field would suddenly be occupied by a vision of his platoon commander walking towards him. This might cease abruptly or go on to loss of consciousness, probably with some generalized convulsion.

In another case (Case 43) the visions were superimposed on the preserved part of the field, which was also still seen clearly, and produced a most bizarre experience. While in the cinema he suddenly saw in the right half-field various objects in the hospital ward. These appeared as a continuation to the right of the screen, on which he could still see the film he was watching to the left. The images were similar in colouring to the pictures on the film. On another occasion, while in bed in the ward, he suddenly saw a motor bicycle and then a convoy of lorries passing from right to left in his right half-field. They appeared to be passing over the end of the bed, which he could still clearly see in the left half-field. On this occasion, the attacks proceeded to a grand mal convulsion.

In another case, the hallucination was more widespread and involved a visual sequence in which the patient was taking part.

Case 21.—In some attacks the left lower (quadrantanopic) field was suddenly occupied by what seemed to be a large white cabbage : the outlines and crenations of the cabbage leaves could be clearly seen. This lasted for a few seconds then consciousness was lost and a grand mal attack ensued. In others, the left field was filled by a snow-covered mountain, which seemed familiar, and as he gazed at it he seemed to be climbing up it, with appropriate changes in its appearance as he climbed. This lasted a few seconds only, and when he seemed to reach the top he lost consciousness and a generalized convulsion occurred.

In all these, although the visual phenomena were strictly unilateral, the discharge appeared to activate a clear-cut memory mechanism. In three, the dominant hemisphere, but in two the minor hemisphere, was involved. These cases, especially perhaps the last two, raise questions of great interest about the organization of " higher " cerebral function. It would seem as if such an integrated and holistic mechanism as memory can at times be fragmentarily activated while still retaining all the qualities of " memory".

In Case 21 the possibility of subjective elaboration of a simple primary hallucination into a more complex scene arises. Here, the hallucination was sometimes of a cabbage, but white not green, and sometimes of a snow-covered mountain top. Both in fact were white, rather amorphous objects. When the latter occurred, the patient felt himself to be climbing, with the contours of the mountain changing as he did so. However, it is not certain whether changes and movement in the original amorphous visual pattern were not interpreted as the visual impressions of climbing up the mountain.

In the other four cases, the hallucinations appeared to fill the whole visual field, though they might start in the defective half. In three, the hallucinations could be recalled and described in detail.

Case 11.—This patient had right adversive attacks leading to generalized grand mal : also sudden right hemianopia followed by flashes of light in this field. On other occasions coloured pictures of various battle experiences in Italy would seem to move across his vision like lantern slides. They filled the whole of his vision and were the prelude to loss of consciousness and grand mal convulsions.

Case 10.—He suddenly saw people he knew and could name at the time, standing round him and telling him to get up. He seemed to be lying down at the time. These figures, three or four at a time, filled the whole visual field and the real visual world was obliterated. The hallucination lasted for a few seconds only and then he lost consciousness and had a grand mal attack.

Case 42.—In addition to attacks of clonic facial movement leading to left adversion and loss of consciousness, this patient had attacks in which he suddenly felt hot, his thoughts seemed to get out of control, and he felt that as if in a dream he was back in Khartoum during the war. He saw and recognized friends around him. The experience was accompanied by strong apprehension and frustration which exactly reproduced the emotions he had in fact felt in 1940 in Khartoum when he thought that he ought to be in England taking a more active part in the war. During this time he could not see real objects around him. The attack led to clonic movement of the face, but very rarely to a generalized convulsion.

In one case, however, although the hallucination was familiar and clearly defined when it occurred, it could not be recalled or described afterwards.

Case 24.—This patient, in addition to left-sided clonic motor attacks, also had two types of visual attack. In one, the remaining right half-field of vision suddenly became blurred so that nothing could be seen clearly. In the other there suddenly appeared in the left (blind) half-field, but spreading rapidly to the right also, the picture of some familiar scene. The picture was in black and white and at the time of its occurrence was clear cut and recognizable, but as soon as it faded only the feeling of familiarity could be recalled. The description here was similar to the " sense of familiarity " of uncinate attacks.

In one case also, the involvement of a memory mechanism seems more fundamental. In this case (Case 42) the whole experience was more mental and less purely visual ; he described it himself as " like a dream ". This contrasts especially with the case (Case 21) where the memory element seems

rather incidental to the primary, rather ill-defined, visual hallucination. It may therefore be seen that epileptic discharge from the parieto-occipital areas provides a wide variety of visual phenomena ranging from crude hallucinations of flashes and coloured lights, through more complex phenomena such as extinction of part or the whole of vision and distortion or disorientation of visual perception, to a highly integrated hallucination of a familiar remembered scene. Some of the problems raised by the kind of attacks occurring in this and the two preceding groups are discussed further below.

Discussion

The content of visual fits shows great variation in minor detail : so much so that in some respects no two fits are alike. Lights may be white, multi-coloured or monochromatic—green, yellow, orange, red, and purple are all described. They may be continuous or interrupted, stationary or moving, varying in intensity, scintillating or sparkling, and of varying shapes. Visual objects may appear smaller or larger than normal, they may seem displaced in space, or simply distorted, strange or unreal, or without meaning as in agnosia. They may appear blurred and indistinct ; or vision may be actually extinguished in part or whole. Formed hallucinations may be in black and white, or coloured. They may be of simple objects or of complex scenes, either static pictures or with movement and action in them. Indeed, there is scarcely any aspect of normal vision which is not represented in one or other of these fits. It is as well to emphasize this variation and complexity, which is in general also a feature of the responses obtained from electrical stimulation of the cortex (Penfield and Jasper, 1954) and to regard it as a reflexion of the flexibility of function of the normal cortex in which discharge from a given cortical point has many possible paths of conduction, depending on the exact state of excitation or inhibition at the various synapses involved.

Nevertheless, it is possible to recognize certain broad similarities in differing fits, and to group them accordingly. Amongst crude hallucinations, these groups may be segregated : (1) Continuous moving lights which may be single- or multi-coloured and of various shapes and patterns, the essential feature being that they are continuous and moving ; (2) continuous, steady, motionless light ; (3) interrupted flashes of light ; (4) negative phenomena—blurring or extinction of vision—form another definite group ; (5) distortions of vision—micropsia, macropsia, apparent displacement of objects, etc.—also emerge ; (6) finally, a number of complex positive phenomena may be seen, consisting of formed hallucinations of familiar common objects or remembered scenes.

Of the whole 60 cases, 31 had crude phenomena of some sort—17 interrupted flashes, 11 continuous moving lights, and three continuous stationary lights—as part of a fit. Twenty-four showed negative phenomena, 11 distortions, and 12 complex hallucinations.

In Table III an attempt is made to relate these six types of fit to the three anatomical groups given above. It appears that crude phenomena of continuous moving lights are especially associated with calcarine lesions. Interrupted flashes seem more common when permanent defects of radiation have occurred, while negative phenomena, distortions, and complex hallucinations seem related to " higher " visual cortex lesions.

TABLE III

PATTERN OF FITS IN THREE MAIN GROUPS OF CASES

Pattern of Fits	Calcarine (9 cases)	Radiation (21 cases)	Higher Visual (30 cases)
Continuous stationary lights	0	1 (1)	2 (2)
Continuous moving lights	9 (1)	1 (1)	1
Interrupted flashes ..	0	11 (1)	6 (4)
Negative phenomena ..	2	6	16 (1)
Distortions	0	1	10 (1)
Complex hallucinations	1 (1)	5 (1)	6

Figures in parentheses denote the number of cases within the total in which phenomena occur *after* another visual phenomenon in a given attack. Total types of fit are greater than total number of cases.

It is usual to associate unformed visual hallucinations with lesions of the occipital pole and calcarine region, and although our findings support such a view, they suggest that some forms of crude visual phenomena are also common with lesions well anterior to the occipital pole and impinging at times on the posterior temporal cortex.

Negative phenomena deserve special consideration. The inhibition or extinction of preceding vision or visual imagery must play an important part in normal visual activity in " clearing the decks " for the next object of visual attention. The cases noted here certainly suggest the possibility of a special anatomical site for such negative activity and raise once more the question of a special visual inhibitory area (area 19 S, McCulloch, 1949) already mentioned by one of us (Russell, 1947) in connexion with the general distribution of epileptogenic wounds. These negative fits may affect a complete half-field but in some cases this spreads rapidly to involve all vision and in others complete visual loss

seems to occur *ab initio*. Such effects, presumably originating in one hemisphere, underline once more the functional integration of the two visual cortices which is an essential part of normal vision, and suggest the rapid transmission of impulses between the two occipital poles. Complex hallucinations also show a similar variety of distribution and spread within the visual fields.

These findings may be compared with those from electrical stimulation of the cortex producing visual effects (Penfield and Rasmussen, 1950; Penfield and Jasper, 1954). Direct stimulation of the calcarine cortex is technically difficult because of its relative inaccessibility, and is recorded in only a few instances, but, in general, responses from this and the nearby cortex of the occipital pole were crude, unformed phenomena of lights of various colours and shapes, but usually with a quality of movement—undulating, quivering, dancing, or glistening were adjectives commonly used. Intermittent flashing lights certainly occurred occasionally from the immediate vicinity of the pole, but these seemed more frequent when stimulation was applied further forward to the lower parts of the lateral occipital cortex. Information about negative phenomena is more scanty. Responses of shadows across vision and areas of "blackness" were occasionally recorded, but the points stimulated were in the lateral aspects of the occipital lobe and did not seem differentiated from those producing crude positive responses. Complex visual hallucinations, involving at times remembered scenes, were obtained from stimulation of points on the lateral aspect of the temporal lobes, both anteriorly and near its posterior extremity, but not from the occipital or parietal areas. These hallucinations were, however, often accompanied by auditory phenomena also, a feature which was not recorded by our patients. Distortions of visual perception, micropsia, macropsia, etc., were also noted, again generally from the temporal cortex.

So far as crude visual phenomena are concerned, therefore, our findings seem in general agreement with the results of stimulation. When formed hallucinations and remembered scenes are involved, however, some of our cases certainly suggest firing from posterior parietal and occipital cortex. Indeed, it is of special interest that these cases involving remembered scenes seem to fall into two distinct groups from the anatomical point of view, for some of the cases have wounds in the temporal lobe, and others have lesions in the posterior parietal or parieto-occipital region.

Cases 43, 44, 23, and 24 are all remarkable instances of temporal lobe visual hallucinations which are often in the contralateral field and often involve the reproduction of remembered scenes or are associated with a feeling of familiarity. These cases may have division of the lower half of the optic radiation (Meyer's loop), or complete hemianopia. In Case 44 the missile has entered just above the radiation on the right and the metal fragment has passed into the posterior temporo-parietal region on the left. There is no dense field defect. It is therefore possible that in this case the hallucinatory phenomena may originate from the left parietal region rather than more anteriorly in the temporal lobe. In none of this group were there any associated attacks with crude visual flashes.

In the other cases (Cases 11, 45, 41, 21, and 42) the wound was usually limited quite clearly to the parietal or parieto-occipital region (Case 21 is difficult to classify), and in three the visual field defect was slight and indicated that the amount of brain damage was slight. In Cases 11 and 45, which fall most certainly into this group, there were also at times crude visual discharges of the type reported in Group II cases.

In most of these cases the hallucinated "memory" could be recalled in exact detail, but in one (Case 24) with a temporal wound and hemianopia, the effect was more of a "*déjà vu*", and, although the hallucinated scene was entirely familiar, its details could never be described.

Here, therefore, is convincing evidence that hallucinations of remembered scenes may originate from two widely separated anatomical areas: first, the temporal lobe, which is well known for its association with a sense of reminiscence and "*déjà vu*", and secondly the posterior parietal or even occipital region which is known to be connected with visual imagery and visual memory.

It is easy to understand that discharge from the parieto-occipital region can lead to formed visual hallucinations, though there is a tradition in clinical neurology that temporal lobe lesions are more often associated with this. However, temporal lobe lesions may involve hallucinations of other special senses with a characteristic feeling of familiarity. There seems, therefore, in this region to be a special function associated with remembering in general which applies to many senses—visual, auditory, olfactory, etc. This may well be a function of the hippocampus and its connexions, and if this is so then when we observe the same complex hallucinations appearing in both temporal and parietal lobe lesions we are in fact seeing the results of stimulating two parts of the same mechanism, or perhaps we are demonstrating that a visual memory depends

not only on a certain pattern in the parieto-occipital region, but that, like other memory processes, its effective functioning depends in some way on hippocampal activity.

A further observation which may have anatomical implications is the strikingly low incidence of visual fits in occipital pole wounds. The calcarine cortex differs from the parastriate and other cortical areas in having no direct thalamo-cortical connexions. Such an area would be expected to have only a small epileptogenic capacity if thalamo-cortical discharges are important for initiating and maintaining or enhancing cortical discharge. The conception of a " centrencephalic " system whose activity plays an important part in elaborating epileptic discharges in the cortex is one which has some support from animal experiments (Jasper and Droogleever-Fortuyn, 1947). The very limited epileptic properties of the injured striate cortex might be considered as further evidence in its favour.

It is interesting that in four cases in this series unformed hallucinations were followed by severe headache, sometimes throbbing and unilateral, the whole sequence resembling what might be called a traumatic migraine. However, we were not able to recognize any special physiological or anatomical features in these unusual cases.

This study provides some evidence both for the quality of activity and method of function of the occipital cortex and related areas. But such findings must be used with discretion in formulating theories of cerebral activity. For when a group of cortical cells fires abnormally the subjective symptoms experienced need not necessarily arise at the site of firing but may be produced in some intact part of the cortex at which the discharge arrives. Moreover, a brain wound may not only give rise to an epileptic focus, it may also interrupt some of the normal channels of discharge from the " firing " area and this may further alter the apparent " function " of the area. The correlation of such evidence as we have brought forward with that derived both from cortical stimulation and non-traumatic extirpation where possible is thus important for a proper evaluation.

References

Bay, E. (1953). *Brain*, **76**, 515.

Brazier, M. A. B. (1951). *The Electrical Activity of the Nervous System*. Pitman, London.

Dewhurst, K. E., and Pearson, J. R. (1955). *Journal of Neurology, Neurosurgery and Psychiatry*, **18**, 53.

Jasper, H. H., and Droogleever-Fortuyn, J. (1947). *Res. Publ. Ass. nerv. ment. Dis.*, **26**, 272.

McCulloch, W. S. (1949). In *Precentral Motor Cortex*, 2nd ed. Ed. Paul C. Bucy. Chapter VIII, Cortico-cortical connections. University of Illinois Press, Urbana, Illinois.

Penfield, W., and Jasper, H. H. (1954). *Epilepsy and the Functional Anatomy of the Human Brain*. Churchill, London ; Little, Brown and Co., Boston.

——, and Rasmussen, T. (1950). *The Cerebral Cortex of Man*. Macmillan, New York.

Robinson, P. K., and Watt, A. C. (1947). *Brain*, **70**, 440.

Russell, W. R. (1947). *Ibid.*, **70**, 225.

——, and Whitty, C. W. M. (1953). *Journal of Neurology, Neurosurgery and Psychiatry*, **16**, 73.

Spalding, J. M. K. (1952). *Ibid.*, **15**, 169.

——, and Zangwill, O. L. (1950). *Ibid.*, **13**, 24.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 97.

THE ARTERIAL SUPPLY OF THE SPINAL CORD AND ITS SIGNIFICANCE

BY

D. H. M. WOOLLAM and J. W. MILLEN

From the Department of Anatomy, Cambridge

It has long been recognized that an adequate blood supply is an essential prerequisite to the normal functioning of the neuron. The major contributions to the study of the vascular architecture of the central nervous system have naturally been based on the examination of the brain. Investigations of the arterial supply of the spinal cord have been few, and have been limited to the examination of human material obtained at necropsy (Adamkiewicz, 1882 ; Kadyi, 1889 ; Tureen, 1938 ; Suh and Alexander, 1939). It appeared therefore that a study of the arterial patterns of the spinal cord based primarily on the use of an experimental animal might serve to elucidate the principles on which the blood vessels are distributed to the spinal cord, at the same time providing additional information concerning the manner of vascularization of the central nervous system in general.

A major obstacle to the study of the vascular arrangements of the central nervous system has been the problem of differentiating the arteries from the veins. Indeed, as recently as 1938, Campbell was obliged to point out that the extensive monograph of Pfeifer (1930) on the angio-architecture of the cerebral cortex suffered from the serious defect that the structures described as veins were in reality arteries and vice versa. The first experimental method which allowed of the certain differentiation of the cerebral arteries and veins was that introduced by Scharrer (1940). In this method the arterial system was injected with a gelatin solution incorporating rice starch, the particle size of which prevented the injection mass from entering the capillaries. Thick sections of the brain treated in this way were immersed in iodine solution, the starch-iodine reaction took place, and the arteries appeared deep black. Using the same technique, the venous system of a similar animal was filled and the results compared.

Scharrer's method, although allowing a clear distinction to be made between arteries and veins, does not enable the whole vascular system, including the capillaries, to be visualized in the same organ. In a previous paper (Millen and Woollam, 1953) a method was described which allows such a differentiation to be made. Briefly the technique was as follows. Blue and red dispersion media were used for the injection. (These media were supplied by the B.B. Chemical Co., Ltd., Ulverscroft Road, Leicester, England, who state that the dispersions were prepared by ball-milling pigments with a small quantity of a highly active surface wetting agent. The blue pigment used was copper phthalocyanine, and the red was a red lake pigment.) When the red pigment was introduced into the heart or ascending aorta it filled the arteries and arterioles, passed on into the capillaries, and filled both the capillaries and veins. The introduction of the blue pigment immediately afterwards at the same site pushed the red pigment on into the capillaries and veins, but the blue pigment did not itself enter the capillaries. By this method a picture of the whole vascular system of the animal could be obtained, in which the arteries were outlined by blue pigment and the veins and capillaries by red. This method was used for the study of the arterial patterns in the rat's spinal cord which is the subject of the present communication.

Materials and Methods

The spinal cords of 16 adult rats were examined. In each case the rat was killed with ether, and 2 ml. of the red dispersion was injected into the ascending aorta through the heart at a pressure of about 80 mm. Hg. As soon as this injection was completed, 3 ml. of the blue dispersion was introduced in a similar fashion. After fixation in 10% formalin for a week, the spinal cord of the animal was dissected free from the surrounding structures and the surface distribution of the blood vessels studied and photographed in colour. Sections were then cut with the freezing microtome at 100 to 200 μ in the transverse, sagittal, and coronal planes at each level of the spinal cord. These sections were rapidly dehydrated in ascending grades of alcohol, cleared in xylol, and mounted in balsam.

In addition, a number of dissecting-room specimens

of human spinal cords were examined. In all of these the arteries were outlined by the injection of red lead.

Findings

The method employed in this investigation enabled a clear distinction to be made between the arteries and veins, for the arteries were filled with the blue dispersion and the veins with the red. The difference in the morphology of the vessels was exactly similar to that which Scharrer (1944) described in the intracerebral vessels, for the arteries ran in smooth, graceful curves and gave off their branches at acute angles, whereas the veins received their tributaries at more obtuse angles.

The spinal cord of the rat receives its major arterial supply from a number of radicular arteries which run along the ventral nerve roots to reach the anterior surface of the cord. Each of these radicular vessels divides near the midline into an ascending and a descending branch (Fig. 1). The ascending and descending branches form a midline chain of anastomoses which run the whole length of the cord from the medulla to the beginning of the filum terminale. The uppermost ascending branch is joined by a descending vessel formed by the union of branches from the vertebral arteries (Fig. 2).

The radicular vessels are derived from arteries in the neighbourhood of the vertebral column and are comparatively constant in their arrangement. Three or four large radicular arteries supply the cervical region of the spinal cord, but, in the thoracic region, the radicular arteries are small in size, inconstant in arrangement, and only two or three in number. In the lumbar region, an extremely large vessel invariably runs along the second or third lumbar nerve root. This vessel is unilateral and most often enters from the right side. It appears to be the sole arterial supply to the whole of the lower lumbar and sacral parts of the spinal cord. This large lumbar radicular artery shows clearly the usual divisions into ascending and descending branches. In the case of this vessel the division occurs quite some distance from the midline and the descending branch is much larger than the ascending branch (Fig. 3).

In the cervical region the anastomoses between the adjacent branches of the radicular vessels are well marked, and the anastomotic chain has at first glance the appearance of a median artery continuing downwards from the anterior spinal vessel formed by the branches from the vertebral arteries. On more careful examination, however, its composition from the ascending and descending branches of the radicular arteries is apparent.

The ascending and descending branches of the thoracic radicular arteries are slender vessels which run considerable distances before anastomosing with each other or with the descending branch of the lowest cervical artery or the small ascending branch of the great lumbar radicular artery (Fig. 1). In consequence the anastomoses between these vessels are of an exiguous nature, and the anterior anastomotic chain is poorly defined and in some instances almost discontinuous over the thoracic part of the spinal cord.

The arrangement of the arterial supply to the anterior surface of the spinal cord of the rat (Fig. 4) may be summarized as follows :—

The anterior surface of the cord is supplied by radicular arteries reaching the cord along the ventral nerve roots. Each of these arteries divides into an ascending and a descending branch, and is primarily responsible for the blood supply to a particular region of the cord. The ascending and descending branches anastomose freely in the cervical region but only to a very slight extent in the thoracic region. The lumbar and sacral parts of the cord are supplied by the branches of the single great lumbar radicular vessel. The smaller ascending branch of this vessel anastomoses poorly with the lowest thoracic descending branch.

Only a small number of human spinal cords have so far been examined. These showed that the arrangement of the radicular vessels is essentially similar to that described for the rat. The vessel described as the anterior spinal artery is in fact a longitudinal anastomotic chain formed by the ascending and descending branches of the radicular arteries in a manner similar to that observed in the rat, rather than a continuous vessel coursing down the anterior midline from the medulla to the filum terminale. The anastomoses in the thoracic region are also, as in the rat, extremely slender.

In each segment of the rat's cord, central branches pass, from the ascending and descending branches of the radicular arteries, into the anterior median fissure to enter the substance of the spinal cord. Because of the distance of the bifurcation of the great lumbar vessel from the midline, some of the central branches of this vessel can be seen coursing over the anterior surface of the cord to gain the anterior fissure (Fig. 3). In general, however, the central branches pass directly downwards into the anterior fissure and have no course outside the nervous tissue. The central branches, as seen in the series of coronal sections, enter the bases of the anterior horns of the grey matter and usually pass alternately to the right and left sides (Fig. 5). On entering the grey matter each vessel breaks up into arterioles which are distributed to the anterior

FIG. 1.

FIG. 2.

FIG. 3.

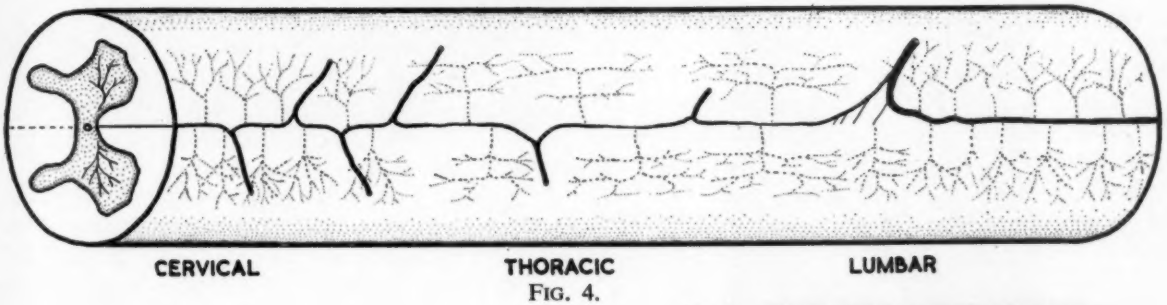


FIG. 4.

FIG. 1.—Anterior surface of injected spinal cord of a rat. Thoracic region. Two radicular arteries are shown dividing into ascending and descending branches. × 4.

FIG. 2.—Anterior surface of medulla and cervical region of injected spinal cord of a rat, showing the contributions from the vertebral arteries to the midline anastomotic chain. × 4.

FIG. 3.—Anterior surface of injected spinal cord of a rat. Lumbar region. The large radicular artery, corresponding to the artery of Adamkiewicz in man, is shown dividing into its two branches. Central branches run on the surface of the cord towards the anterior median fissure. × 4.

FIG. 4.—Diagram illustrating the arrangement of the anterior radicular arteries, the midline anastomotic chain, and the distribution of the central arteries in the spinal cord of the rat.

FIG. 5.—Coronal section through the cervical region of the injected spinal cord of a rat, showing the alternate distribution of the central branches. × 16.

FIG. 5.

FIG. 6a.

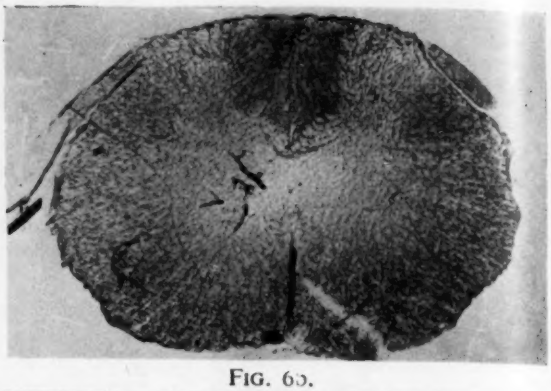


FIG. 6b.

FIG. 7.

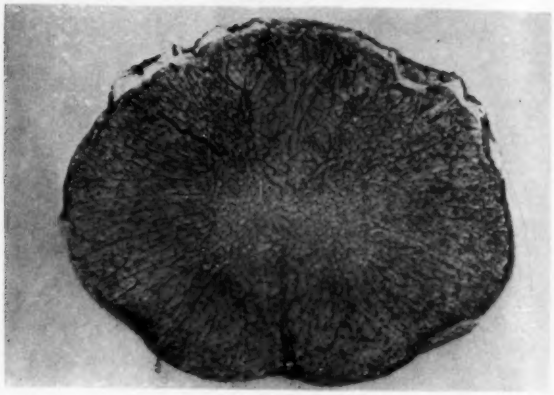


FIG. 8.

FIG. 6.—Transverse sections through the injected spinal cord of a rat. × 16. (*a*) central artery running in the anterior median fissure to the base of the anterior horn ; (*b*) the distribution of the central branch in the substance of the grey matter.

FIG. 7.—Posterior surface of the injected spinal cord of a rat. The anastomoses between the posterior radicular arteries are in the form of irregular loops. × 7.

FIG. 8.—Transverse section through the injected spinal cord of a rat, showing a branch from a posterior radicular artery entering the posterior horn of the grey matter. × 16

and lateral horns and the basal part of the posterior horn (Fig. 6).

The density of distribution of these central branches varies from region to region of the cord. Thus in 1 cm. of the cervical cord 12 central branches are distributed to each side ; in 1 cm. of the lumbar cord 17 branches go to each side, whereas in the same length of the thoracic cord only seven central branches are given off on each side. Because of the long distance separating the central branches in the thoracic region, their manner of distribution differs from that of the other regions. In the lumbar and cervical regions the branches are distributed in a compact, bushy manner, whereas in the thoracic region they trail away horizontally and are less closely packed (Fig. 4).

In addition to the anterior anastomotic chain, there are two smaller anastomotic chains situated on the posterior aspect of the rat's spinal cord in relation to the dorsal nerve roots. These are much less constant in their situation than the anterior anastomotic chain, and they form irregular loops between each other and in their individual courses (Fig. 7). They are formed by radicular vessels which arise from the arteries in the neighbourhood of the vertebral column and reach the postero-lateral sulcus by passing along the dorsal nerve roots. Central branches arise from these posterior arteries and pierce the tip of the posterior horn of grey matter (Fig. 8) to supply that part of the posterior horn which is not supplied by the central branches of the anterior vessels. The central branches of the posterior arteries are very restricted in their distribution and travel upwards and downwards only to a limited extent. The density of distribution of these branches in the various parts of the cord closely parallels that of the anterior central branches.

Discussion

There are no descriptions in the literature of the arterial supply of the spinal cord in mammals other than man, but in current textbooks of human anatomy an anterior spinal artery is described which starts above by the union of branches from the vertebral arteries and traverses the cord to its lower extremity, being reinforced by a succession of small contributions from vessels in the neighbourhood of the spinal cord. In such descriptions the main emphasis is placed on the median artery on the anterior surface of the spinal cord, and the radicular arteries are relegated to a secondary position. In the rat, as the illustrations show, there can be little doubt that there is an arterial anastomotic chain formed entirely by the anterior radicular arteries with the exception of the upper cervical part of the chain which is formed by the anterior spinal branches of the vertebral arteries. Each of these anterior radicular arteries divides into ascending and descending branches which anastomose with a branch from the next significant radicular artery above and below. The examination of the human spinal cord made during the course of this investigation suggested that a similar arrangement is present in man, and in this respect amplified the views of Suh and Alexander (1939). The clearest illustration of the manner in which the anterior anastomotic chain is formed is seen in the illustration of the large lumbar radicular artery of the rat (Fig. 3), which corresponds to the arteria radicalis anterior magna described by Adamkiewicz (1882) in man. The fact that central branches supplying the grey matter of the spinal cord are given off from this artery from the point of its division well away from the midline leaves little doubt that it represents the equivalent in the rat of the artery described as the " anterior spinal artery " in most textbooks of human anatomy. The examination of human material made during the course of this investigation confirmed that the arrangements are essentially similar, and indicated that the lower thoracic, lumbar, and sacral regions of the cord receive their blood supply from the ascending and descending limbs of the arteria radicalis anterior magna of Adamkiewicz which is the " anterior spinal artery " of anatomical textbooks or " truncus arteriosus anterior " of Suh and Alexander (1939) in this situation. Furthermore this particular artery serves to show to a marked extent a point, which is also borne out by examination of the thoracic and cervical regions of the cord, that the arterial supply of the spinal cord is from a series of individual arteries which anastomose with each other rather than from a " truncus arteriosus anterior " replenished by a succession of small radicular contributions.

The question arises as to the normal direction of blood flow in the midline anastomotic chain. Inferiorly there can be little doubt that the blood must flow upwards and downwards respectively in the ascending and descending branches of the artery of Adamkiewicz, so that from the point of division of this artery blood flows downwards to the lumbo-sacral enlargement of the cord and upwards to the thoracic region. Superiorly the vertebral artery corresponds very closely to the artery of Adamkiewicz, differing largely in the fact that it is bilateral. Its large ascending branch meets that of the opposite side to form the basilar artery and its descending division joins its fellow of the other side to form the anterior spinal artery, in which the blood must flow downwards to the cervical region of the cord to meet blood entering the anastomotic chain in the ascending branch of the first significant cervical radicular artery. It is evident therefore that the blood flow in the midline anastomotic chain is by no means all in one direction, from above downwards, but that it flows in opposite directions at different levels. It follows from this that several water-sheds are produced at points more or less equidistant from the point of division of the large radicular arteries into ascending and descending branches. Such water-sheds are most evident in the mid-thoracic portion and at the junction of the thoracic cord with the cervical and lumbar regions.

Experimental injections into the vessels of the human spinal cord have produced curious and inconsistent findings. Thus, when making injections into the human spinal cord at various levels, Tanon (1908) found that, whereas he could fill the vascular system of the entire cord from injections made into the lumbar vessels, injections into the thoracic portion above the ninth segment filled only small stretches, and in the cervical region the territory injected from each artery was only slightly larger. On the other hand Suh and Alexander (1939) found that injections from above could only be made into the cervical region and from below only into the lumbar and thoracic regions. They considered that this was because the anastomoses between the arteries of the cervical and upper thoracic regions were so thin as to be inadequate. Apart from possible criticisms of the technique and injection media employed, the discrepancies between these observations may well be explained by the effects of post-mortem clotting in the vessels and the trauma inevitably associated with the removal of the spinal cord from the cadaver. It is not unreasonable

therefore to conclude that it is undesirable for inferences to be drawn as to the normal direction of blood flow in the midline anastomotic chain from the behaviour of injection media introduced after death at a single point into the vascular system of the isolated human spinal cord.

In the thoracic part of the spinal cord of the rat, the midline arterial anastomosis is not only narrow with few slender radicular contributions, it also sends relatively few central branches into the substance of the cord. This arrangement is similar to that described in the human spinal cord by Suh and Alexander (1939) and Herren and Alexander (1939). Because of this arterial pattern Suh and Alexander (1939) have suggested that the vulnerability of the thoracic region of the spinal cord in certain diseases is due to the fact that the thoracic region has a relatively poor blood supply. Scharrer (1944) sought to explain the early vulnerability of the hippocampus in carbon monoxide poisoning by the rake-like arrangement in which the arteries supplying the hippocampus come off the main stem. He believed that in the rake-like system there tended to be a fall in pressure towards the end of the main artery, whereas in the dichotomous system the pressure was even throughout the system of ultimate branches. The diagram (Fig. 4) shows how the situation of the thoracic cord resembles that of the hippocampus, and it may well be argued that the blood pressure is lower in the thoracic part of the cord than in the other parts. Suh and Alexander (1939) believed that the early susceptibility of the thoracic cord in subacute combined degeneration could be explained by the anoxic effect of pernicious anaemia on the nervous system, and the consequent early involvement of those parts where the blood pressure was lowest. The lesions, however, which appear in the thoracic cord in this disease are lesions of the fibre tracts, and the capillary bed appears to receive no arterioles in the white matter, the white matter being supplied from the capillary bed of the grey matter. If anaemia was the cause of the damage to the white matter, one would expect the grey matter adjoining it to be equally affected. It would therefore seem unlikely that the pathology of subacute combined degeneration of the cord can readily be explained on a vascular basis.

Gerard and Serota (1936) have concluded that the amount of blood reaching a neuron varies with the degree of activity of the part of the body it supplies. The arterial supply of the spinal cord of the rat seems admirably designed to fit this principle. The cervical and lumbar regions of the cord which subserve the regions capable of the greatest activity, the limbs, are supplied with major arteries catering for their specific requirements, while the thoracic region may perhaps be regarded as taking the blood that is left over from both. Although it is obviously justifiable to comment on the manner in which a concentration of blood in the cervical and lumbar regions of the cord is achieved, there is no reason to assume as a natural corollary that the blood supply of the thoracic region is inadequate.

The examination of the arterial patterns of the spinal cord of the rat reveals two significant features. First there is the fact that the motor neurons of the spinal cord are all supplied from the same anterior anastomotic chain. Secondly there is the manner in which the arterial supply of the spinal cord of the rat exactly parallels that of man. This second observation suggests that the spinal cord of the rat affords an excellent site for study and experiment upon the general significance of the vascular supply to the central nervous system.

Summary

The arterial patterns of the spinal cord of the rat were studied by means of a technique in which, from an injection into the aorta, the arteries were filled with a blue dispersion and the veins and capillaries with a red. The arterial supply of the rat's spinal cord was found to bear a close resemblance to that of the human cord. From a midline anterior anastomotic chain formed by anterior radicular arteries central branches supply the anterior and lateral horns and the basal parts of the posterior horns of grey matter. This supply is less rich in the thoracic region than it is in the cervical and lumbar regions of the cord, a finding which may be related to the differing metabolic requirements of the various regions.

We wish to express our gratitude to Professor J. D. Boyd for his advice in the preparation of this paper. Our thanks are also due to Mr. T. R. L. Brooks for the photographic work.

References

Adamkiewicz, A. (1882). S.B. Akad. Wiss. Wien. Math-nat. Kl. Abt 3, **85**, 101.
Campbell, A. C. P. (1938). *Res. Publ. Ass. nerv. ment. Dis.*, **18**, 69.
Gerard, R. W., and Serota, H. (1936). *Amer. J. Physiol.*, **116**, 59.
Herren, R. Y., and Alexander, L. (1939). *Arch. Neurol. Psychiat., Chicago*, **41**, 678.
Kadyi, H. (1889). *Über die Blutgefässe des menschlichen Rückenmarkes.* Gubrynowicz and Schmidt. Lemberg.
Millen, J. W., and Woollam, D. H. M. (1953). *J. Anat., Lond.*, **87**, 114.
Pfeifer, R. A. (1930). *Grundlegende untersuchungen für die Angioarchitektonik des menschlichen Gehirns.* Springer, Berlin.
Scharrer, E. (1940). *Anat. Rec.*, **78**, 173.
——(1944). *Quart. Rev. Biol.*, **19**, 308.
Suh, T. H., and Alexander, L. (1939). *Arch. Neurol. Psychiat., Chicago*, **41**, 659.
Tanon, L. (1908). Thèse de Paris, No. 98. Vigot Frères, Paris.
Tureen, L. L. (1938). *Res. Publ. Ass. nerv. ment. Dis.*, **18**, 394.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 103.

ENCEPHALITIS IN LOA-LOA FILARIASIS

BY

L. VAN BOGAERT, A. DUBOIS, P. G. JANSSENS, J. RADERMECKER, G. TVERDY, and M. WANSON

From the Medical Clinic and the Laboratory of Parasitology of the Institute of Tropical Medicine, and the Laboratories of Pathological Anatomy and Electroencephalography of the Institute Bunge, Antwerp

"*L'étude des filarioses offre encore maints aspects inconnus dont l'examen réserve à ceux qui s'y consacreront des observations captivantes.*"

J. RODHAIN (1953)

Filariasis is usually regarded as a benign disorder and its neurological manifestations have rarely attracted attention. This may be due to the frequency with which the malady is superimposed upon other diseases with meningo-vascular involvement, to which the fatal complications have been attributed. Viewing the scene from a greater distance, we have felt that these complications might be related to filariasis itself. The subject is of some importance in view of the increasing availability of highly potent anti-filarial drugs.

REVIEW OF THE LITERATURE

The first *Loa loa* was extracted from the eye of a negress in 1770 by Mongin at San Domingo. The disease was described in West Africa by Guyot in 1777 as quoted by Lorenz (1890) and by Manson later (1904).

In 1908, Broden and Rodhain reported that in exceptional cases they had found a filarial embryo in the cerebrospinal fluid, admitting the possibility that a blood vessel had been injured by the needle.

The same year, Külz (1908) reported that in the Cameroons he had observed for four months a patient showing all the motor and psychiatric manifestations of sleeping sickness, but in whom it had not been possible to demonstrate the trypanosome in the blood or cerebrospinal fluid, or by lymph node puncture. The results of inoculation were negative and treatment was without effect. The blood of Külz's patient (not the cerebrospinal fluid as quoted by Chalgren and Baker, 1946 and 1947) was swarming with microfilariae.

Brunetière (1913) recorded a case with paralysis of the tongue and hand followed, seven months later, by paralysis of the entire left side of the body. He envisaged the possibility of a terminal filarial (mf. Loa) embolism of the sylvian artery.

In 1919, Robles noted in acute onchocercosis at Guatemala the possibility of profound prostration, delirium, convulsions, trigeminal involvement, and intermittent sweating. He also described a case of chronic onchocercosis with epilepsy resulting from perforation of the skull by a tumour.

Anderson's (1924) report from British Guiana was more complete. His case concerned a coloured girl aged 7 years affected by filariasis, who presented at necropsy a marked cerebral congestion with pericapillary leucocytic infiltration. He found numerous microfilariae (*M. bancrofti*) of normal appearance in the cerebral and cerebellar vessels. This was the only case of the six he reported in which he was able to make a post-mortem examination. He classes the frequency of microfilariae in the different organs in this order : kidneys, lungs, spleen, brain, liver, cerebellum, and myocardium.

Tha Mya (1928) reported a case with hemiplegia and contracture of the arm following a coma lasting four hours. There were unidentified microfilariae in the cerebrospinal fluid, which also contained blood. Microfilariae have also been recovered from the cerebrospinal fluid of an advanced case of trypanosomiasis (Chambon, 1933, *M. perstans*) and from the sheath of the optic nerve in a young Mexican Indian woman (Giaquinto Mira, 1934).

Rodhain (1937) recalled that in Hissette's case he had observed *M. perstans* in the capillaries of the choroid plexus. (Chalgren and Baker in 1946 refer wrongly to this case as one of onchocercosis with meningeal involvement.)

Meanwhile Peruzzi (1928) had observed cerebral filariasis in five monkeys suffering from trypanosomiasis, and Hashimoto (1939) found a microfilaria in the vessels of the anterior lobe of the pituitary of a dog.

There exists, however, experimental work which is little known, that of Wail, Popow, and Prjadko (1926). It concerns guinea-pigs infected with *Dioptholriaena tricupsis Fedschenko* 1874. This parasite was found in the capillaries which were permeable though filled with the filariae. They

described acute neuronal lesions, with neuron aphasia, phantom cells, and proliferation of the pericapillary glia. The lesions were thought to be due to disturbance of the capillary circulation dependent in turn upon the mechanical and obstructive effects of the microfilariae and to the toxic effect of the metabolic products of the parasites. This work is the first in which neuropathological studies of the disease were carried out with modern techniques.

The possible appearance of neurological and psychiatric symptoms in microfilariasis is now well recognized and several reports have appeared in recent years. That of Bonnet (1943) concerned a man of 42 years whose illness had begun five days before coming under observation, with rigors, fever, headache, and vomiting; this was accompanied, two days before admission, by torpor interrupted by periods of agitation. On admission, his respiration was rapid and there was a marked meningeal syndrome without any apparent motor defect, but with absent knee and ankle jerks and a right-sided Babinski response. Lumbar puncture yielded a fluid with 26 cells and 40 mg. of protein. There were no trypanosomes but 5 to 6 *M. loa* per field. A thick drop of blood showed *M. loa*. The blood urea was 170 mg. and the urine contained 0·25 g. of albumin per 100 ml. He died three days later with hyperpyrexia. He showed an aortitis probably due to old syphilis, of which, however, there was no further evidence. In this case the unilateral Babinski response probably indicated an accentuation of the lesions in the one hemisphere.

Bonnet related the meningeal syndrome in his patient to the filariasis but believed that the finding of microfilariae in the cerebrospinal fluid was fairly common. It is admitted, he said, that they are too bulky to pass the meningeal barrier and that it is the needle that introduces them into the subcutaneous tissues or into a small vessel. The frequent finding of red blood cells in the cerebrospinal fluid and the small number of microfilariae that one finds there is in favour of this interpretation. However, contamination by a needle is improbable even in the case of *M. loa* and *perstans* which invade the circulation, since the blood contains few of these parasites: three or four is the maximum in a thick drop. In any case injury to a vessel is rare during lumbar puncture and Bonnet believes that the passage of the parasites is the result of damage to the vessels by another disease. He emphasizes only the meningeal syndrome in his article; he leaves in the background the severe involvement of the central nervous system revealed by a symptomatology that we shall meet again later.

In his book, Napier (1946) mentioned "the possibility of psychoneurotic disorders". The possibility of a cerebral invasion was also mentioned by Chalgren and Baker (1946).

Bertrand-Fontaine, Schneider, Wolfromm, and Cagnard (1948) reported a case with double hemiplegia and a progressive course, reacting to treatment with "hetrazan". The patient was a man aged 30 years without previous illness, who developed a progressive hemiplegia, though in the course of its development there were several remissions. It was accompanied by periods of confusion and agitation with variable and transient ocular signs. There was a partial regression of symptoms spontaneously and then an improvement with treatment. The patient had an old loasis with oedema, marked eosinophilia in the blood, subjective ocular symptoms, a positive intradermal reaction, and living *M. loa* in the peripheral blood.

During the first few hours of treatment the symptoms increased, but after three courses of 3799 R.P. there was a considerable improvement suggesting that the symptoms arose from the filariasis. The cerebrospinal fluid was normal. As for the mechanism of the neurological signs, the authors were undecided as to whether there was an adult filaria in the subarachnoid spaces at the base of the brain (localization of choice) or whether there had been a migration of microfilariae in the vascular bed, causing obstruction with an oedematous reaction.

In their work of 1950, Kenney and Hewitt give as psychoneurotic manifestations of loasis, insomnia, headache, nervous depression, and abnormal irritability. The report is based on four observations. The first concerned a man aged 28 years with a change in personality accompanied by torpor. These symptoms were sufficiently severe for him to return to Europe. During this leave he again suffered from headache with acute mental symptoms and an eosinophilia varying from 50 to 56%. The removal of a worm (*M. loa*) from the eye led to an amelioration of all his symptoms and a fall in the eosinophilia to 3%. In the second case the symptoms were less marked and were also improved by extraction of the filaria. These two cases in Europeans were caused by *Loa loa*. The third case concerned an Indian suffering only from depression. The fourth was a negro in whom irritability and abnormal aggression, accompanied by a right hemiplegia, appeared suddenly. These two cases were caused by *M. bancrofti*. A state of apathy followed the initial symptoms. With "hetrazan" treatment the headache increased, and there was mental confusion and vomiting. He died on the seventh

day. There was no necropsy. These last two cases were observed in Central America.

In 1952, Kivits reported four new cases with "invasion of the cerebrospinal fluid" by *M. loa*. His first case was that of a woman who had suffered several times from headache and after a loss of speech had entered into coma. Lumbar puncture showed 50 vigorous living microfilariae per c.mm. of cerebrospinal fluid. She died in hyperpyrexia after five days in coma.

His second observation concerned a woman who had had an abscess in the popliteal fossa for 15 days and then suffered convulsions followed by coma; there was generalized hypertonia and myosis. The optic fundi were normal. The cerebrospinal fluid contained 18 microfilariae per 50 c.mm. Four days later she died with hyperpyrexia. At necropsy, there was oedema of the pia mater with flattening of the convolutions and, on section, punctate haemorrhages without gross haemorrhage or softenings. Histologically, Kivits described foci of infiltration, with occasional small necroses, giant cells, and a few haemorrhages. In one area, microfilariae were found inside a giant cell. Some foci were perivascular. The choroid plexus and pituitary were free from abnormality.

His third case was that of a girl of 13 years with mental confusion, choreoathetoid movements, and generalized tendinous hyperreflexia, more marked on the right. The cerebrospinal fluid showed 8 actively motile microfilariae per 50 c.mm. At the end of four days the patient died with a temperature of 38° to 39° C. terminally.

The fourth case was that of a boy aged 12 years, with a history of six days of progressive prostration with generalized hypertonia. The first lumbar puncture showed 6 microfilariae per c.mm., 8 cells per c.mm., and 20 mg. per 100 ml. of protein. Two days later there was somnolence with myosis. Lumbar puncture then yielded a fluid with 48 white cells, 4 red cells, and 4 microfilariae per c.mm. The fluid improved, containing first 3 and then 1 microfilariae per c.mm. but it remained bloodstained. He died 17 days after admission in a deepening coma.

There are thus four cases in which coma, accompanied by hypertonia, appeared suddenly followed by death in four to seven days. In a single case there were focal cerebral signs in the form of choreoathetoid movements. Only in the last case was the cerebrospinal fluid bloodstained. In the remaining cases the microfilaria had not modified its composition.

We see no reason for putting the cases of encephalitis in a separate group. They also consist of an acute neurological syndrome, with the characteristics of a vascular disorder sometimes manifested as hemiplegia. In Kivits's last observation, as in Tha Mya's case, microfilariae were found in bloodstained fluid.

Kivits also wondered how the microfilariae had penetrated into meningeal spaces. The patients, all of whom were negroes, were not suffering from trypanosomiasis. It was not known whether they were syphilitic, but in view of the age of two of them (12 and 13 years), it is difficult to envisage meningovascular syphilis. He wondered whether a pre-existing encephalitis might not facilitate the passage of the microfilariae. Their presence would then be fortuitous. He noted, however, that at the time that he observed these cases there was no encephalitis in the Mayumbe.

In considering these observations as a whole, two questions immediately spring to mind. The first is the significance of microfilariae in the cerebrospinal fluid; the second is that of the structural basis of these severe neuropsychiatric manifestations, the majority of which are fatal and without any suggestion that an active treatment has provoked the symptoms.

(1) The fact that the cerebrospinal fluid remains normal in composition when microfilariae are present (Hissette, 1932; D'Hooghe, 1935; Manson-Bahr, 1950) and that in proved filariasis, lumbar puncture often yields a normal fluid (Pourbaix, 1952, quoted by Janssens, 1952) suggests an accidental penetration. The presence of microfilariae in the cerebrospinal fluid does not, therefore, in itself constitute a meningeal syndrome. One must also envisage the role of accessory factors such as meningovascular inflammations at the base of the brain favouring the penetration of the microfilariae in the monkey (Peruzzi, 1928) and even in man (Chambon, 1933); syphilitic lesions facilitate the passage of microfilariae not only into the cerebrospinal fluid but also into the parenchyma of the brain. The lesions of the vessels in these cases invite the penetration of the vessel wall. The coexisting meningeal reaction permits the microfilariae to remain in an environment normally unfavourable to them.

(2) As far as the anatomical basis of these states is concerned, we have only the reports of Wail and others (1926), Anderson (1924), and Kivits (1952) on which to build a hypothesis. From the clinical point of view, we have distinguished meningeal (Bonnet's main observation, 1943) and psychiatric disorders (Kenney and Hewitt, 1950) but above all cerebrovascular syndromes, sometimes focal (Brunetière, 1913; Mme. Bertrand-Fontaine and her

collaborators, 1948) with a bloodstained fluid (Tha Mya, 1928) and sometimes presenting as a coma of insidious onset but steadily progressing to a fatal end.

It will have been noted earlier that in certain cases (observation 4, of Kenney and Hewitt, 1950, for example) the initiation of the modern treatment for the disease is followed, at first, by an exacerbation of the neurological and psychiatric signs, as if the therapeutic lysis of the parasite gave rise to an acute toxicosis. On the other hand, if one views the fatal cases as a whole, it is clear that the " natural " evolution in certain cases, especially in young patients, follows a constant pattern. Since the general effects of filariasis (fever and urticaria) are at present considered as allergic manifestations (Napier, 1946), may not the cerebral signs also be interpreted as the effects of individual neural sensitization ?

We first report the clinical and electroencephalographic observations and then discuss the visceral and neurological lesions.

CASE REPORT

The patient, aged 34 years, was a man of unusual strength (height 6 ft. and weight 14 st. 6 lb.). He had been repatriated eight months before the end of his second term on account of a variety of complaints, especially a loss of weight (30 lb.) in three months, dyspepsia, and repeated bouts of dysentery.

The illness began with malaria, bacillary dysentery, and furunculosis during his first term spent in the east province of the Congo constructing roads as a supervisor of public works. The second term was spent in the Bas-Katanga. This time he had three attacks of bacillary dysentery, and was particularly troubled by echythematous lesions which were still present when he arrived at hospital. Albuminuria had been observed in Africa but was not considered of importance.

Clinical examination showed a slight enlargement of the liver, the lower border of which descended about 3 cm. Both the liver and gall bladder were tender. The spleen and other abdominal organs seemed normal. The breath sounds were harsh but there were no rales. The heart sounds were muffled and there was a slight reduplication of the second pulmonary sound. An exercise tolerance test gave a normal result. The blood pressure was 125/80 mm. Hg. The pulse was 80 per min. Electrocardiographic examination (Dr. G. R. Vleeschoouwer), on the other hand, showed a moderate sinus bradycardia, a *coeur couché*, with marked left ventricular preponderance (angle −15°). The auricle P wave was of normal form and duration but P3 was inverted, the P-Q interval 0·16, and the ventricular Q-R-S complex of normal duration 0·07, broadening of R in D2, Q-R-S inverted in D3 ; D1-D3 were mirror images. The S-T interval was normal. The T wave was reversed in D3. The perfectly symmetrical, mirror-like appearance of Q-R-S in D1-D3, even in the absence of alteration of this complex in D2, suggested an arterial and especially a coronary cardiopathy.

Radiographs of the chest confirmed the presence of a large heart with left ventricular hypertrophy. The lung fields were clear but there were heavy hilar shadows. Examination of the urine showed 100 mg. % of albumin but no reducing substances were noted. The specific gravity was 1026 and the *p*H 6·5. The deposit contained hyaline and granular casts, abundant microfilariae, but no red blood cells. A second examination two days later showed, in addition to much mucus, a deposit containing red and white cells, numerous small round cells and two granular casts, and a pure growth of *Streptococcus faecalis* (Dr. Brutsaert).

Tests of renal function were satisfactory : phenol-sulphone-phthalein 62% and urea clearance 126%. Intravenous pyelography was entirely normal.

A blood examination gave the following results : Thick drop, *M. loa* +++, haemoglobin, 16·4 g. (103%), red blood cells, 4,841,000 ; volume index 1·07 ; volume of packed red cells 48% ; colour index 1·1 ; diameter of red blood cells 84 ; basal sedimentation rate, 25 mm. in one hour (Westergren) ; leucocytes, 8·200 (eosinophils 15·5%, non-segmented neutrophils 0·5%, segmented neutrophils 55%, lymphocytes, 25%, monocytes 2%). The Mazzini, Wassermann, Kahn, and Kline reactions were negative.

Analysis of urine gave urea, 35 mg. ; uric acid, 4·5 mg. ; total protein, 8·19 g. ; total cholesterol, 300 mg.

Tests of hepatic function showed thymol turbidity to be 7·77 ; zinc sulphate (Kunkel) 9·03 ; calcium sulphate, +1 in distilled water 9·03 ; cephalin-cholesterol (Hanger), Lugol, ++.

The bromsulphthalein test was negative and the provoked elimination of galactose 0·4 g.

A routine neurological examination was negative apart from abolition of the right knee jerk which, the patient declared, dated from an accident to the knee at football.

A diagnosis was made of hyperfilarization with disturbance of the proteins, together with intestinal infestation by schistosoma, giardia, and oxyuris.

The patient was admitted on March 19, 1953, felt definitely improved by the rest, but later his wife informed us that he had suffered for several days from violent headaches. He received at the same time as his wife a tablet containing diethyl carbamazine, 50 mg., and 22·5 mg. of histaphene maleate (Carbilista U.C.B.). On March 20, he was given a tablet three times, on March 21 and 22, the same dose, on March 23 again one tablet in the morning, a total of 550 mg. for the five days. The day after the first dose, the patient complained of headache and violent pain in the left flank with the characteristics of renal pain. On March 20, in the evening the temperature was 99·4° F. The next two days the patient's condition and temperature were the same. On the evening of March 22 the temperature rose to 100·2° F. On March 22, in the hope of diminishing the reaction, he was given at 6 p.m. and 10 p.m. a tablet of " postaphène ". During the day of March 23, he felt worse, the headaches were almost intolerable, especially

at the back of the neck ; he complained of mistiness of vision and a desire to vomit.

Until this moment, the reactions appeared reasonable considering the severity of the filarial infection, and we had under observation an almost perfect control in the wife, who had received for the same filariasis the same doses at the same times. We stopped the specific therapy after the morning dose, but again gave a tablet of " postaphène ".

In spite of stopping the treatment, his condition slowly deteriorated during the night and on the morning of March 24 he passed from somnolence into coma. This we attributed, rightly or wrongly, to the histamines. According to his wife he had not had hallucinations, or disturbance of speech, or convulsions. He slowly and progressively lost consciousness. Since the coma was accompanied by slight stiffness of the neck, a lumbar puncture was performed on the morning of March 24 with considerable difficulty as the patient was struggling violently. The fluid was clear and colourless (total protein 30–35–38 mg.). The Pandy test was negative, the Weichbrodt reaction ++, and the Lange curve 11222100000. The microfilariae obtained by lumbar puncture as well as those in the circulating blood were incontestably *M. loa*. They possessed all the essential morphological characteristics and also had an unusual structure, namely a central body. Finally, they showed evidence of attenuation by the diethyl carbamazine.

On March 13, Dr. E. van de Briel reported slight conjunctivitis and slight dryness of the conjunctival mucosa. The corneae were normal on examination with the corneal microscope. The media were transparent and the visual fields normal. Visual acuity was 10/10 in both eyes. A second examination on March 25 showed normal eyes with normal fields.

On March 24 at 5 p.m. he was semi-comatose but could easily be aroused by pinching his skin and could be made to put out his tongue. His face and head were red and swollen ; the latter was slightly retracted but in the midline. He did not show any involuntary movements. The tendon reflexes were absent. The plantar responses were flexor but difficult to obtain. The abdominal reflexes were present but feeble. The masseteric reflex was present. The left limbs seemed more hypotonic than the right. It was impossible to elicit a voluntary movement but at the moment of lumbar puncture, the patient protected himself with both hands. There was no Lasègue sign. On the other hand, there was a characteristic stiffness on trying to flex the neck.

The eyes were in a central position. Automatic movements were possible but not voluntary movements. The pupils were equal and reacted briskly. The corneal and conjunctival reflexes were present and the patient blinked when pain was caused by pressure on the infra-orbital branch of the trigeminal nerve. On command, the tongue was protruded forwards in the mid-line, but not beyond the dental border. It appeared to be parched. The right facial muscles contracted less well than the left and there was the same asymmetry in the contraction of the palate. The sensory and motor functions of the trigeminal nerve could not be assessed. According to his wife, there was no difficulty in swallowing. He was incontinent of urine but not of faeces ; the bladder was not palpable.

On March 25 his general condition was about the same, but he was breathing more stertorously. He had more difficulty in swallowing. Babinski's sign was not present. There was no marked hemiplegia, and the weakness of the left limbs was no greater. The fundus oculi was normal (Dr. van de Briel).

At this time we made a diagnosis of acute meningo-encephalitis, probably an acute haemorrhagic and oedematous encephalitis reminiscent of the so-called post-salvarsan encephalitis which often showed the features of a brain purpura. We imagined that such a picture might also occur with multiple emboli.

Fresh examinations of the blood on March 24 and 26 showed that microfilariae had disappeared from the peripheral blood. The haemoglobin had fallen to 14·8 g. (92·5%), there were 4,760,000 red blood cells, the colour index was 0·96. The volume of packed red cells was 45%, volume index 1·04, the mean cell diameter was 7·5, and the sedimentation rate more than 50·5 mm. in one hour. The leucocyte count was 11·2 with a fall in the eosinophils to 1·5% and a neutrophilia of 84%. There were only 9·5% lymphocytes and 5% of monocytes. The urea had risen to 78 mg., the uric acid remained at 4·8 mg. There was 1·9 mg. of creatinine ; the non-protein nitrogen was 54 mg. The total protein was 8·47 g. and the cholesterol 333 mg.

Examination of the urine showed 0·46 g. albumin per 100 ml. with a specific gravity of 1045 and a *p*H of 6. This time there was much urobilinogen and the deposit contained numerous hyaline and granular casts and red blood cells but only a few microfilariae.

In spite of classical treatment the patient became progressively worse and the coma deepened. His temperature was 101·6° F. on the evening of March 25. The next morning there was in addition a pulmonary oedema which overcame the patient after a few hours. He died in hyperthermia (105·4° F.) at 4 p.m.

In summary, our patient, although of an unusually strong constitution, returned from Africa in a state demanding attention ; there had been loss of weight, digestive disorders, exacerbated bacillary dysentery, and a subacute nephritis with cardiac and moderate hepatic failure. He showed a hyperfilariasis with *Loa*.

On admission, he complained of nausea and violent headaches which became worse with the institution of treatment and were accompanied by pain in the left side and kidneys. The patient complained of a mist before the eyes ; he became somnolent and then comatose. Death occurred six days after the start of treatment and three days after the appearance of the first poorly localized but severe signs of involvement of the nervous system.

An electroencephalogram (Fig. 1) recorded on March 25 showed almost continuous bursts of slow irregular waves of 1½ to 3 c. per sec. reaching 120 μv., and most marked in the anterior and temporal leads. From time to time, and especially when the patient became more drowsy, a rhythm of 6 c. per sec. and 50 to 120 μv.

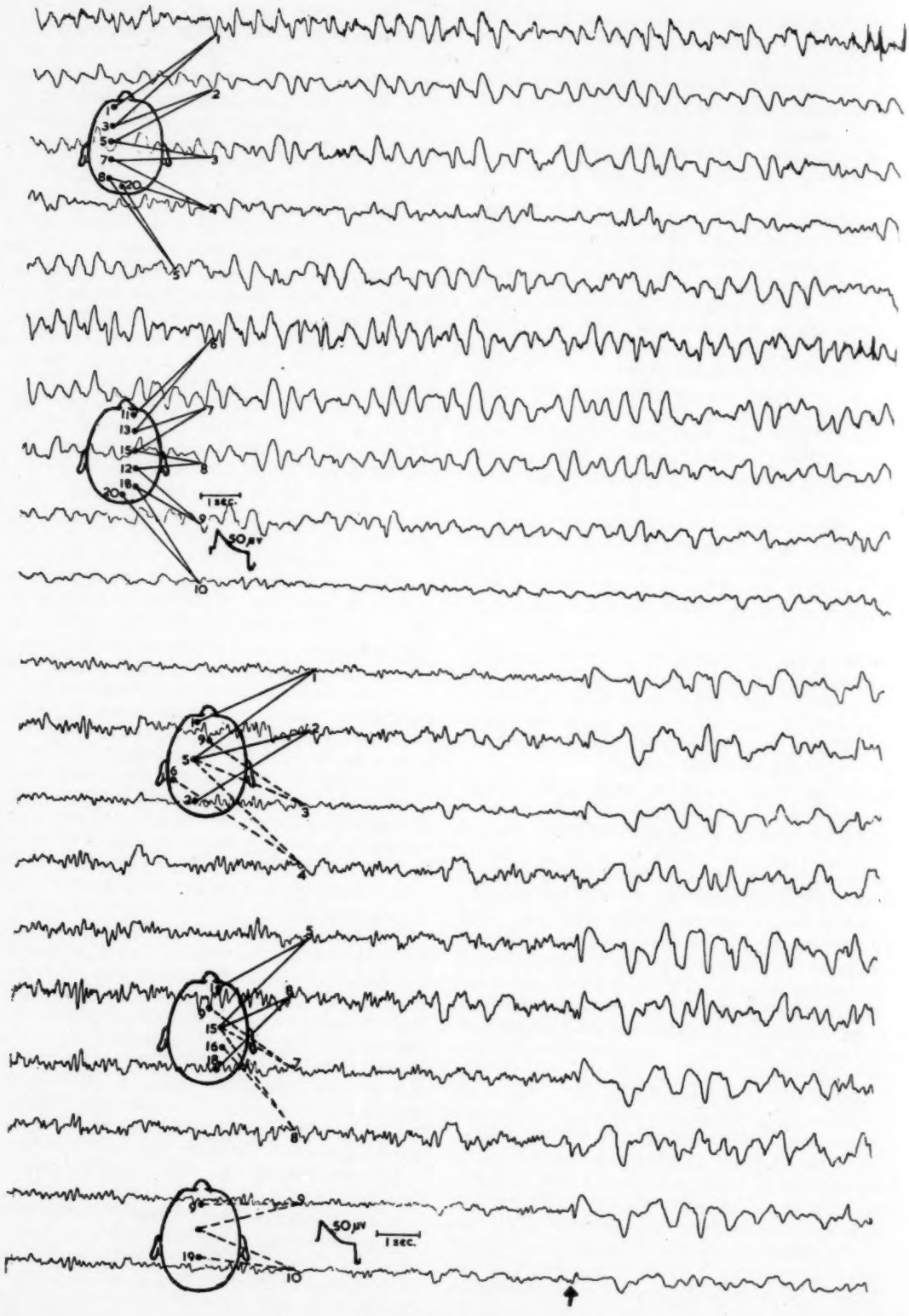


FIG. 1.—E.E.G. records.

appeared in all leads ; there were also some even more rapid waves reaching 7 to 9 c. per sec. but not exceeding 30 μv. When an external noise was made a burst of very slow waves—1½ to 2 c. per sec.—appeared and was often preceded by a flattening of the tracing ; the patient then relapsed into drowsiness and the 6 to 7 c. per sec. rhythm again became dominant. When the noises became louder and one attempted to rouse the patient the first recorded tracing, very disorganized and very slow, reappeared. With the intravenous injection of 50 ml. of hypertonic saline, numerous muscular potentials appeared mixed with the slow and irregular rhythm of the base. There was scarcely any improvement in the record, but the patient awoke and brought up a considerable amount of wind.

Dr. Radermecker reported as follows :

" This is a grossly abnormal record with symmetrically distributed, very slow polymorphous delta waves. When the patient went to sleep and began to snore, this type of record gave place to a basal rhythm of more rapid and synchronized waves at 5 to 6 c. per sec. The tracing indicates a diffuse and deeply situated encephalitic process. The modifications of the rhythm in the course of sleep recalls the synchronization which is encountered in very young children."

NECROPSY REPORT

Necropsy was performed 17 hours after death by Dr. Tverdy.

The body was that of a well built man in a good nutritional state. The lungs were severely oedematous and showed slight purulent bronchitis. The heart was dilated and filled with blood, the myocardium pale and flabby, with petechiae on the endocardium, slight atheroma of the coronary arteries, and normal valves. The liver was larger than normal and with a marked lobular pattern, but normal biliary passages. The spleen was moderately enlarged with a wrinkled capsule showing many petechiae and a pitted surface. The pulp was black in some areas and brown in others. It did not yield to the knife. The Malpighian corpuscles were not very obvious. The gastric mucosa was atrophic, had lost its folds, and showed many petechiae. The thyroid was large and fleshy. The kidneys were of normal size, the cortex smooth and a little pale, and the cortical vessels congested. The bladder, ureters, and adrenals appeared normal. The aorta was slightly atheromatous. The brain and the spinal cord were removed and fixed *in toto*.

No adult filariae were found in the loose connective tissue of various organs nor in the subcutaneous tissue of this very fat man.

Histology of the Organs

Kidneys.—The proximal convoluted tubules are severely degenerated, the cells being greatly swollen so as to obliterate the lumen almost completely. The nuclei scarcely take the stain while the brush border is almost everywhere defective. The nuclei of the distal nephron, however, are preserved. There are occasional red blood cells and hyaline casts in the tubules. The glomeruli show a definite increase in nuclei, this cellularity being partly due to the presence of polymorphonuclear leucocytes and partly to a proliferation and turgidity of the endothelial cells. The basement membrane is not thickened. The capsular cells of some glomeruli have hypertrophied and desquamated. The walls of some arterioles show fatty infiltration. There are microfilariae in the intertubular capillaries in the glomerular loops and in the tubules (Fig. 2).

Lungs.—There is oedema and intra-alveolar haemorrhage, severe vascular congestion, and desquamation of alveolar cells loaded with carbon pigment. Within the vessels there are irregular cells suggesting at first sight giant nuclei 20 to 40 μ long by 5 to 10 μ broad.

Liver.—Frozen sections stained with sudan stain show a moderate centrilobular fatty infiltration. The portal spaces are heavily infiltrated with lymphocytes, histiocytes, and a few polymorphonuclear leucocytes. In some areas the cellular infiltrations surround necrotic foci containing the microfilariae (Fig. 3). These foci develop into fibrous nodules (Fig. 4). In the adjacent sinusoids in contact with the walls of the centrilobular veins there are multinucleated giant cells. The biliary canaliculi in the portal spaces often contain bile casts. Occasionally there is a slight atrophy of the periportal parenchyma, followed by proliferation of fibrous tissue so that a few parenchymal cells within the enlarged portal spaces are cut off. Outside the portal spaces there are cellular infiltrations which are sometimes associated with the presence of microfilariae.

Heart.—The interstitial tissue of the myocardium shows the same cellular infiltrations as those seen in the liver, with lymphocytes, histiocytes, and here and there a few polymorphonuclear leucocytes. In the midst of the infiltrations there are microfilariae. The cardiac fibres are fragmented. The fibrous tissue is thickened at the expense of the atrophying muscular fibres with a resulting moderately severe perivascular fibrosis.

Adrenals.—Cellular infiltrations are found in the medulla and cortex similar to those seen in the heart and liver, sometimes associated with the presence of microfilariae.

Spleen.—In several areas, especially under the capsule, there are foci of necrosis in the centre of which are large numbers of microfilariae. The

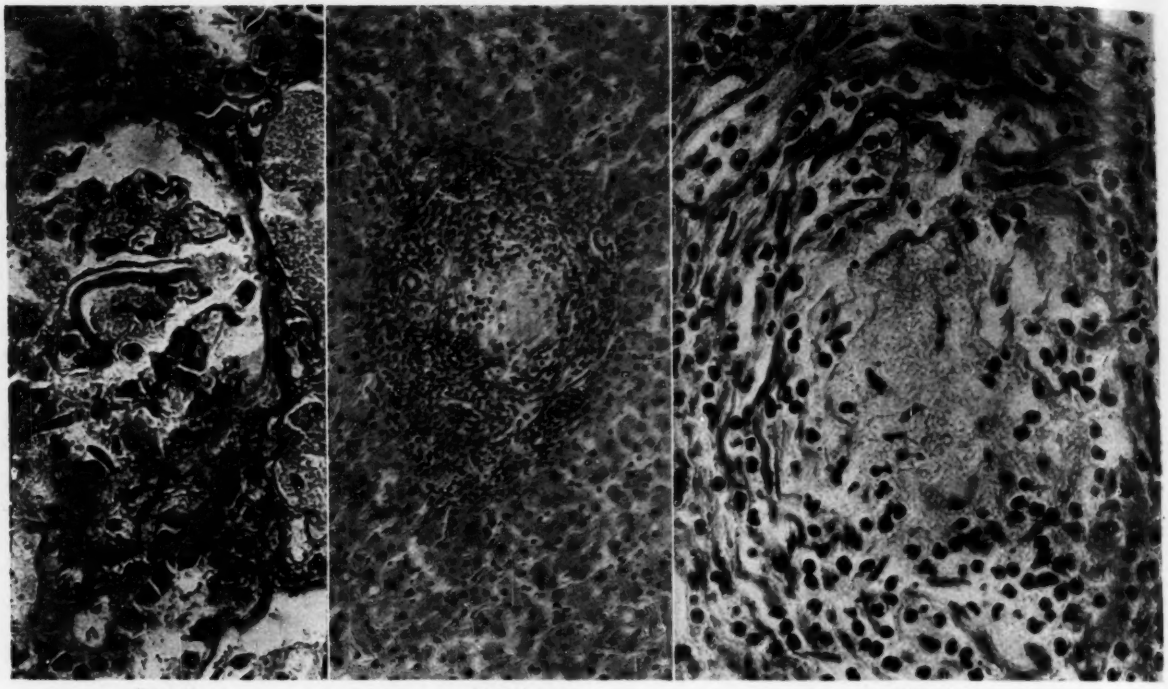


FIG. 2 FIG. 3 FIG. 4

FIG. 2.—Kidney, showing a microfilaria in one of the tufts of a glomerulus. There is also cloudy swelling of the proximal convoluted tubule. Haematoxylin and eosin.

FIG. 3.—Liver showing necrosis in the centre of a portal space.

FIG. 4.—Debris from microfilariae in the centre of an area of necrosis.

necrosis is limited by a zone of fibrous reaction. Within the fibrous tissue there are several multinucleated giant cells. There is a diminution in the cells of the germinal centres, those remaining lying in an acidophil, fibrillary substance. The sinusoids are poorly demarcated and the endothelial cells as well as those of the pulp are enlarged. Within the sinus as well as the trabeculae of the pulp there are moderate numbers of plasma cells.

Lymph Node.—A lymph node taken at the bifurcation of the trachea shows severe congestion ; the sinuses are distended and filled with histiocytes, polymorphonuclear leucocytes, and endothelial cells. The germinal centres show the same changes as were seen in the germinal centres of the spleen.

Considering the histological findings as a whole, the microfilariae pass the vascular barrier and penetrate deeply into the tissues. Their presence seems to cause, in the spleen and the liver, for example, a central necrosis followed by a peripheral fibrous tissue reaction with formation of multinucleated giant cells.

The subcapsular region of the spleen is particularly affected. In the liver, the necrosis associated with the presence of microfilariae is located in the portal spaces. With older lesions, fibrosis takes the place of necrosis. As well, the bile canaliculi are plugged with bile casts, without jaundice or macroscopic changes in the biliary passages. In the liver the picture is completed by the appearance of giant cells in the vicinity of the centrilobular vein and sometimes in the portal spaces. In other sites (myocardium, suprarenal glands) the microfilariae cause a reaction characterized by aggregations of lymphocytes and histiocytes. The passage of the microfilariae through the glomerular tuft produces very little reaction. The changes in the kidney are most marked in the proximal convoluted tubules, the picture in fact being that of a nephrosis rather than of a nephritis. In the foci of necrosis and tissue reaction, the microfilariae fragment before disappearing, but nowhere is there any evidence of parasitic phagocytosis.

In the extra-cranial organs two types of lesion can be demonstrated : (1) Nodular infiltrations of lymphocytes and histiocytes with a few polymorphonuclear leucocytes, usually in the vicinity of a microfilaria ; (2) foci of necrosis, probably due to the presence of microfilaria. The latter can be found in various stages of degeneration without giving rise to any phagocytic reaction. These foci are surrounded by a zone of inflammatory and

FIG. 5

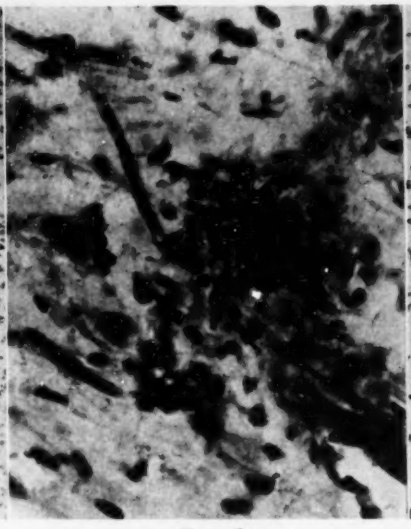


FIG. 6

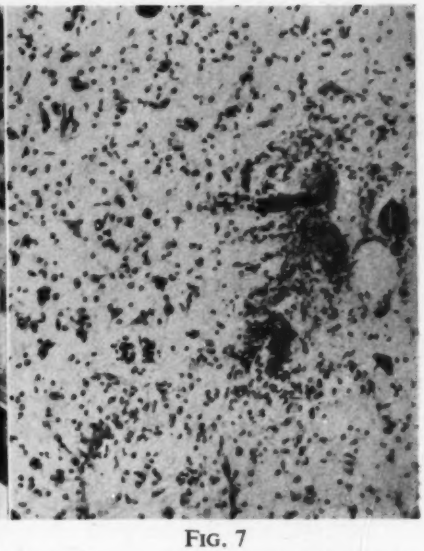


FIG. 7

FIG. 5.—Coronal section of brain passing through the superior frontal convolution. The lesions are of moderate severity. The meninges are patchily infiltrated, especially in the vicinity of a heavily cuffed vessel. The moderate-sized veins are surrounded by cuffs which at intervals show fusiform enlargement. On the left there is a small granuloma. Some capillaries and small veins show a marked stasis with lymphocytic cuffing. There are a few ghost nerve cells and also cells with ischaemic degeneration. There is a moderate diffuse microglial hyperplasia. Nissl.

FIG. 6.—Hippocampus. There is a nodule in the middle of the pyramidal zone close to a vessel stuffed with microfilariae (below and to the left, they appear like faggots in the lumen of the vessel). There are microfilariae lying free in the tissues. The nerve cells show ischaemic degeneration. There are regressive changes in the neuroglia. Frozen section, stained with cresyl violet.

FIG. 7.—N. reticularis. General view of a commencing diffuse perivascular reaction. The remainder of the section shows numerous microglial cells and satellitosis of the small nerve cells. Frozen section, stained with cresyl violet.

fibrous tissue reaction. With increasing age of the lesion, the cellular elements give place to fibrous tissue. Multinucleated cells participate in the reaction. Between the two types of reaction there are all intermediate grades ; the small granulomas with central necrosis and the cellular nodules cause little change in the parenchyma in which they lie. They injure without doubt the myocardial muscle fibres and the periportal tissues. At a distance from these focal lesions a more diffuse reaction is observed, but it is difficult to prove a relationship with the principal disease. The finding of the microfilariae constantly in the neighbourhood of the nodules or in great numbers within the necrotic foci strongly suggests that there is a relationship between the two types of lesion and the presence of the embryos of the parasite. We have not been able to show the parasite in the lungs.

Examination of the Nervous System

Naked-eye Examination of the Brain.—Moderately severe meningitis was found over the convexity and particularly around the interpeduncular and cerebellar cisterns, the vermis, and the sylvian fissures. The meninges were markedly adherent at the Pacchionian granulations. There were no obvious vascular lesions. The optic nerves appeared normal. The olfactory bulbs were turgid.

On coronal section of the brain, there was a tendency to petechial haemorrhage equally marked in the cortex and centrum semi-ovale. It was rather less marked in the thalami and around the third ventricle. There were no softenings but there were greyish areas in the peduncle and the tegmentum of the pons. At the level of the inferior olives the whiteness of the latter was striking. In the roof of the fourth ventricle there were abnormal greyish streaks around the ependymal canal and the neck of the medulla.

In summary, there was little to be seen apart from focal vascular changes and an accentuation of capillary stasis, sometimes with small diapedeses of red cells in the cerebral hemispheres, cerebellum, and brain-stem, and a pearly appearance of the olives.

Histology of the Brain.—The distribution of the lesions has been demonstrated by a series of blocks cut in the coronal plane embedded in celloidin and stained with cresyl violet. The first block passes through the prefrontal region. There is a meningeal reaction, especially in the neighbourhood of the veins. Beneath the infiltrated meninges the molecular layer shows the moderate glial reaction one would expect. Occasionally there is exuded plasma.

The cytoarchitecture of the cortex is everywhere recognizable (Fig. 5). There are pericapillary infil-

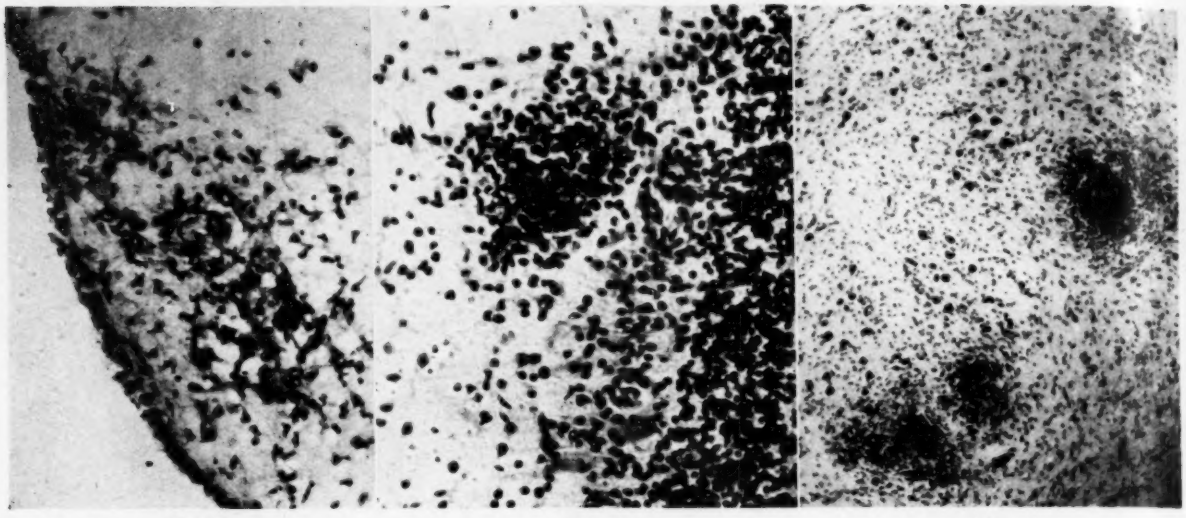


FIG. 8. FIG. 9. FIG. 10.

FIG. 8.—Thalamus. Subependymal infiltration. In the centre there is again a dilated capillary with its wall packed with cells and a few microfilariae ; on the left there is only a network of debris ; the infiltration consists of microglial cells, lymphocytes, and, occasionally polymorphonuclear leucocytes (frozen section, stained with cresyl violet).

FIG. 9.—Cerebellum showing granuloma in the molecular layer, composed of lymphocytes and an occasional polymorphonuclear leucocyte. No microfilariae can be seen. Homogenizing cell change in the adjacent Purkinje cells (on left). Nissl.

FIG. 10.—Brain-stem at the level of the inferior olives. Several granulomas are visible to the naked eye. Nissl.

trations, but on the whole it is the veins of medium size that are surrounded by cuffs which may be very thick and either discoid or fusiform in shape.

All intermediate forms between infiltrating processes and granulomatous nodules can be seen. The perivascular infiltrations are particularly prominent in the third and sixth layers of the cortex and in the subcortical region. They are equally developed in the depths of the sulci and the summits of the gyri ; they can also be seen, but less frequently, well within the molecular layer.

The same infiltrations are present also in the white matter. In their centres there are concentric spongy zones several times the width of the vessel, and usually staining yellow with Nissl, no doubt due to a hyaline change in the ground substance around an affected vessel. Indeed, there are quite frequently within the vacuolated areas vessels with hyaline walls, thickened eccentrically, or, on the other hand, a vessel surrounded by a lymphocytic exudate of no great density.

A smaller block passing through the anterior part of the basal ganglia shows several foci in the thalamus, in the globus pallidus—especially the inner segment—and in the parts of the caudate nucleus bordering on the ventricule. The claustrum is intact. The insular cortex shows the same changes as the frontal region, but they are less severe. The substantia innominata is intact.

A more caudal block shows a few more foci distributed within the thalamus. The red nucleus and the substantia nigra are intact. The nucleus of Luys is lightly affected ; there, as well as in the internal capsule, a few infiltrations are seen. The putamen and external capsule are intact. There is a very light infiltration of the medial geniculate body. The choroid plexuses, enclosed within the hippocampal sulcus, show an increase in the nuclei in their taeniae. The plexuses themselves show no changes. The cortical infiltrations become less frequent on passing from the superior to the middle temporal convolutions. They can still be found, though in far fewer numbers, in the inferior temporal, fusiform, and hippocampal gyri. They are present in all parts of the white matter. In certain parts, for example, in the digitate white matter of the supramarginal gyrus, there is an extensive infiltration with a softened centre. In other areas, for example, the inferior temporal convolution, the glial infiltrations follow the fibre tracts. The meningeal reaction is most severe over the lobule and precentral convolution. At the outer ends of the sulci the dilated vessels are often ensheathed in well developed cuffs. The striothalamic vein shows the same perivascular cuffing.

The hippocampal gyrus is free from gross change in its architecture. The fimbria and white matter of the hippocampal gyrus show numerous infiltrations. The fascia dentata and pyramidal zone are severely affected. Severe ischaemic or acute lesions are seen in the pyramidal layers together with microglial hyperplasia and pericapillary cuffing with a variety of cells, nodules, and even free microfilariae (Fig. 6).

There are also a few infiltrations in the peri-aqueductal grey matter (Fig. 7). The insertion of the choroid plexus shows a moderate increase in nuclei. There is a granular ependymitis with, in parts, a desquamation of the ependyma. The infiltrations are not, however, very intense in the subependymal region (Fig. 8). There are a few foci of infiltration where the fibres of the centrum semi-ovale enter the corpus callosum. In the white matter underlying the inferior temporal convolution, there is a diffuse glial infiltration and pericapillary infiltrations spreading from the digitate white matter into the centrum semi-ovale.

In the cerebellum the structure of the cortex is everywhere preserved. There is a discrete lepto-meningitis with a few foci of infiltration in the molecular layer, in the midst of the granular layer, or at the point of branching of foliae. Occasional lamellae show the atrophy encountered in vascular disorders. In the vicinity of the small granulomas (Fig. 9) in the molecular layer, there are glial bush formations indicating that Purkinje cells have disappeared. In the white matter nodular infiltrations are particularly to be seen near the " V " fibres in the dentate nucleus itself and in the hilum of this nucleus. The dentate nucleus also shows a diffuse gliosis. There are a few nodular infiltrations at the junction of the pons with the midbrain, especially in the reticular nucleus, the oculomotor nuclei, the median nucleus of Reil, and the pontine nuclei situated close to the raphe. The marginal region of the pes pedunculi and the ventral nuclei are intact.

There is a slight aqueductal granular ependymitis with some infiltrations.

The brain-stem is not severely affected. In the pons there are numerous small foci in the nucleus of the mesencephalic root and in the reticular zone, but there are fewer in the tectum than in the crus. Moderately severe, sheet-like infiltrations are to be seen in the ventral nuclei of the pons and in the pyramidal tracts. Section through the upper part of the medulla shows a few infiltrations in the olives and in the floor of the fourth ventricle. On the whole, existing structures are not destroyed. There are also small foci of infiltration in the pyramidal tracts, in the reticular substance, in the lateral nuclei of the medulla, and immediately beneath the ependyma of the floor of the ventricle. They have everywhere the same appearance. The olives show a moderately severe diffuse gliosis (Fig. 10). A few of the nerve cells in these nuclei show acute changes. In the upper part of the medulla both pyramids show a few glial stars ; there are more prominent foci in the middle cerebellar peduncle, in the superior olives close to the facial nerve, and in the nuclei of IX and XII. The appearances are similar in the lower part of the medulla. Here there are nodules in the intercellary nuclei, the lateral nucleus of the medulla, and the dorsal para-olive. At the cervico-medullary junction there are a few infiltrations in the nuclei of the posterior columns and in the substantia gelatinosa of Rolando. The roots themselves show only a moderate infiltration. In the cervico-medullary region and sacro-lumbar part of the spinal cord the infiltrations are situated most prominently in the pyramidal tracts and to a lesser degree in the grey matter and nuclei of the posterior columns. Sections stained for myelin show everywhere the same changes. The spongy foci described in the centrum semi-ovale appear in these sections as a mushroom-like budding centred on a blood vessel. The myelin has been lysed throughout these polycyclic pale areas. Near these foci there are simple haemorrhagic softenings revealed by pallor of the myelin sheaths involved in the areas of diapedesis. It is easy to distinguish these two types of lesion from each other. They are not the result of celloidin embedding, for they can also be seen in frozen sections stained with Spielmeyer, but here the borders are less sharp. The olfactory bulbs show occasional infiltrations. The dura mater is intact. The pituitary and pineal glands and the stalk of the infundibulum, the chiasma, and the optic nerves are normal.

Muscles.—The fibre bundles, the interfascicular connective tissue, the intramuscular nerves, and the vessels show no abnormality in any of the five pieces of muscle examined.

The peripheral nerves (sciatic, external popliteal, ulnar, radial, and an intercostal nerve) show no loss of myelin sheaths, while sections stained with scharlach R reveal no products of degeneration. There is some infiltration of the perineurium, especially around the vessels, by haematogenous elements which have penetrated the perivascular connective tissue. This exudate is uniform and consists largely of lymphocytes, with a few large mononuclear cells and occasional plasma cells. The walls of the capillaries are particularly rich in nuclei, while the endothelial and adventitial cells also have very darkly staining nuclei with numerous well impregnated chromatin fragments. Nowhere are there any microfilariae. Spinal ganglia and the ganglion of Gasser are normal.

The distribution of the inflammatory lesions may be summarized as follows. In the cortex and the centrum semi-ovale, the focal perivascular infiltrations are found in all areas. Nevertheless, there is a predominance of lesions in the medial surface of the frontal lobes, the paracentral lobule, the frontal and

ascending parietal, inferior temporal, and fusiform convolutions. Of the basal ganglia, the thalamus and the inner segment of the globus pallidus are the most affected. The dentate nuclei, inferior olives, and the nuclei of the floor of the fourth ventricle are similarly involved. In the spinal cord, infiltrations are particularly to be found in the posterior horns and lateral columns. The spinal roots show patchy, moderate infiltration. The spinal ganglia and the muscles are spared. With careful searching lymphocytic infiltrations can be found in the peripheral nerves.

The Structure of the Histopathological Process

A general view of the cortex shows at once that the cytoarchitecture is preserved, a diffuse and uniform microgliosis with red cells, a series of small foci of infiltration with necrotic centres and perivascular situation, and an abnormal visibility of some capillary branching with, in places, little clusters of adventitial cells. A fair number of nerve cells, especially in the vicinity of the perivascular foci, show acute cell change, namely, disappearance of the Nissl bodies, abnormally prominent and swollen dendrites, sometimes a vacuolation of the cytoplasm at the periphery of the cell, and an early pyknosis of the nucleus. In addition there are a few phantom cells. The rod cells, which are noticeable throughout the cortex, rarely show degenerative changes except in the necrotic foci, where both the microglial and oligodendroglial satellites are increased in number. The astrocytes show little reaction, but are sometimes markedly and diffusely increased in layers II and VI and in other regions (thalamus, pulvinar, and hypothalamus).

The vascular lesions are striking; they affect particularly the veins and capillaries. The vessels are much more prominent than usual; within their distended lumen red blood cells piled *en rouleaux* indicate stasis.

The lesions around the veins are more marked than those around the arteries. This can be seen when both types of vessel are present in the one focus. For example, in the hippocampal gyrus one may see a vein with a thinned-out hyaline wall with scarcely visible nuclei and a microfilaria apparently passing across it. The artery is less affected; the adventitial space is filled with plasma or there is the loosely attached debris of an adventitia infiltrated with haematogenous elements, histiocytes, compound granular corpuscles, and microfilariae.

The foci of infiltration and necrosis are of different types according to their stage of development: (1) The walls of veins and capillaries can no longer be seen and are replaced by a series of cells with eosinophil cytoplasm and a large, lobed vascular nucleus (histiocytes), nuclei of lymphocytes, activated microglial cells, a few cells, probably polymorphonuclear leucocytes, and runs of red blood cells. One can also see the interrupted filaments of the microfilariae. (2) The endothelial cells of the capillaries are turgid, their lumen being occupied by festoons of microfilariae (Fig. 11). The adventitial space can only be recognized with difficulty, for within it are the same cells described above. Within the syncytium formed by them are vacuoles either empty or packed with red blood cells or nuclear debris. Some of the cells in these foci show degenerative changes. Microfilariae may be seen with one of their ends within a granuloma while the other lies free in the parenchyma. (3) The appearances resemble those just described but there are also dense intra- and extra-adventitial lymphocytic

FIG. 11.—Aggregations of microfilariae in the lumen and on the surface of the vessels in the upper part of the photograph. They can also be seen in the capillary on the left, and below a microfilaria can be seen leaving the largest vessel. Frozen section stained with cresyl violet.

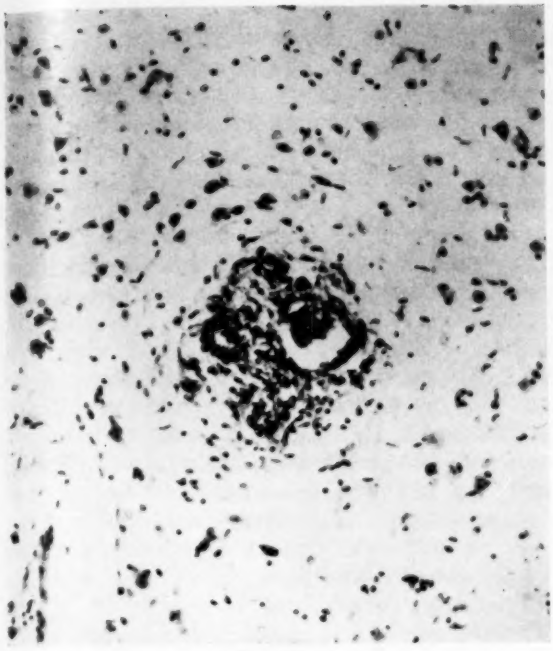


FIG. 12a

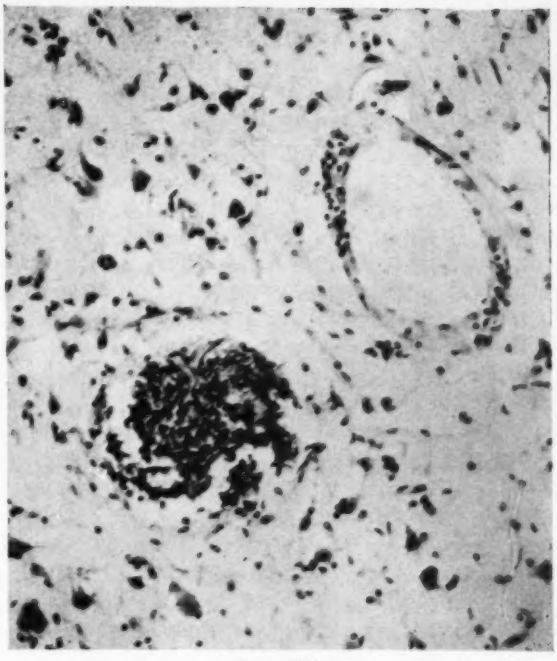


FIG. 12b

FIG. 12.—(*a*) Precentral convolution: early stage in the formation of a granuloma. Several microfilariae can be seen (frozen section, cresyl violet). (*b*) Precentral convolution; granuloma at a more advanced stage in its formation. There are several microfilariae (frozen section, cresyl violet).

infiltrations. (4) The infiltrations may form an actual granuloma around, or, more often, to one side of, a vessel. The lumen of the vessel may be still recognizable but occupied by an adherent thrombus (Fig. 12), or it may be completely unrecognizable (Fig. 12b). Within the granuloma the cells lose their distinctiveness while the nuclei show degenerative changes, but everywhere one can recognize the lacework of the microfilariae.

Within the centrum semi-ovale there are similar granulomas. Where the plasma is coagulated within the vessels, there is marked cavitation of the adjacent parenchyma. Other areas show a spongy liquefaction. On one side of the vessel there is a triangular or oval honeycombed area in which the delicate trabeculae take the blues so as to appear slightly violet. The vessels may be central or represented only by a skein of fibrin filaments, its wall being no longer recognizable. Its fragments are mixed with sheets of glial and haematogenous cells, together with fragmented glial nuclei and free microfilariae.

Aggregates of nuclei can be seen within agglutinated masses of protoplasm where there are abundant microfilariae. These syncytiae correspond to the giant cells mentioned in the literature. The glial or histiocytic origin of these giant cells we regard as debatable.

In some areas, such as the basal ganglia and the hypothalamus, the nerve cells are more affected; hyperchromatosis with shrinkage and loss of dendrites, a hyaline appearance of the cytoplasm and apical dendrite, a turbid vacuolar degeneration and an increase and degeneration of the satellite neuroglia are all noticeable. In these regions there is a diffuse increase in microglia and also of astrocytes, which have large clear nuclei and are to be found in isolated groups. The situation is the same in the cerebellum; the Purkinje cells have, in places, a hyaline appearance.

The leptomeninges show focal infiltrations mostly related to the adjacent parenchymatous foci, so that the microfilariae occupy the capillaries of the molecular layer of the cerebellum and the foci are in the Purkinje cell layer. There are unmistakable nodules swarming with microfilariae immediately beneath the ependyma.

Regarding the lesions as a whole, one may classify them as follows: (1) Very prominent lesions associated with vascular stasis with evidence of vasoparalysis, oedematous transudation, thrombosis and a spongy state, especially in relation to the capillaries and small veins; (2) Nodular infiltrations with adjacent necroses expanding into small spherical granulomas around degenerating blood vessels packed with microfilariae. The nodular or

fusiform infiltrations, the spongy change in the ground substance and the vascular changes due to vasoparalysis are all interrelated. They are always found together and it is this association of lesions that gives the disease its distinctive character. (3) As the foci are disseminated throughout the brain above the peduncle, without predilection for white or grey matter (though the former may be little affected), the reaction of the parenchyma to the effects of the circulatory disturbance is microgliosis with rod cells, a macroglial proliferation, and involvement of nerve cells varying according to locality. The nerve cells only occasionally show neuronophagia. Nowhere are there large areas of cellular devastation. There is an increase in satellites and apparently reversible changes in the cytoplasm. (4) Finally there are sheets of microglia spreading out in a fantail manner near vessels undergoing necrosis or showing reactive changes in their walls, in which can be seen lymphocytes, plasma cells, and polymorphonuclear leucocytes. In their neighbourhood there is neuronophagia, acute nerve cell changes and a diffuse micro- and macro-glial proliferation.

DISCUSSION

Viewed as a whole, the encephalitis under discussion presents the following picture.

Large numbers of microfilariae are present in the lumen of the vessels and insinuate themselves into the smallest capillaries. Nevertheless, we have nowhere seen any histological changes suggesting the purely mechanical effects of obstruction, such, for instance, as the ring haemorrhages characteristic of traumatic fat embolism, of which the fatal outcome is often as rapid as in the case under discussion.

The microfilariae traverse the wall of the vessels, and are also to be found in the adventitial space. They are without any doubt to be found in the parenchyma but always in the vicinity of necroses where it is difficult to say whether or not the vessel wall had been lysed. They produce no reaction in the adventitial space.

In fact the reacting elements of the Virchow-Robin space appear to ignore their presence. We did not find them within giant cells or isolated histiocytes. They are to be seen, however, grouped together in granulomas and in the glial syncytia, but it is impossible to say whether they are within the cells or simply agglutinated within the granuloma. In the vessels and in the parenchyma they are present in large numbers, but always free and little changed as far as one can judge by their appearance and outline.

Yet the microfilariae assuredly cause a violent but well localized gliomesenchymal reaction, of which the spherical granulomas described in the report are the most typical. The glial infiltrations whether sheet-like, *en bouquet*, or nodular as well as the subependymal pericapillary glial networks, are expressions of the same reaction. These glio-mesenchymatous reactions have a tendency to rapid necrosis. The other changes in the ground substance, namely, spongy degeneration with honeycomb appearance, " rain-drop " microcavitation and concentric spongy appearance with or without glial reaction, the diffuse glial infiltrations with a delicate capillaritis in the centrum semi-ovale, and the cellular rarefactions in the pyramidal layer of the hippocampus, all can be regarded as evidence of a functional disorder of the circulation. All this suggests that the granulomatous, nodular, parenchymatous reaction is only a response to a toxin derived from the microfilariae, whether or not the latter are present in enormous numbers in the circulation and whether or not the beginning of their therapeutic lysis has initiated an exceptionally violent and generalized reaction on the part of the organism.

The visceral lesions are similar to those that we have shown in the central nervous system. Here also there are necroses or granulomatous reactions tending in their centres towards necrosis. The microfilariae are intact or in course of fragmentation or lysis. In the central nervous system it is not possible to demonstrate fragmented forms but some have a retracted and atrophic appearance suggesting that they have died. Such appearances are accompanied by diffuse changes, which are probably related to the final toxaemia or to oedematous reactions with the same origin. The necrogranulomatous changes appear, particularly from the histological evidence in the extra-cranial organs, to be not of recent origin but to have preceded the terminal event. The presence within their centres of the remains of microfilariae indicates that they are almost certainly reactive.

It may be asked whether the patient had not succumbed to the combined effects of a microfilarial invasion together with some other cerebrovisceral granulomatous process. This recalls the hypothesis put forward by other observers that the microfilariae would only pass through the blood-brain barrier if this had been damaged by some other infection, for example, trypanosomiasis or syphilis. The fact that the embryos of the parasite found within the granulomas were more or less digested is strongly suggestive of a connexion between their lysis and the reactive process.

An attempt at integrating the cerebral " accidents " can only be achieved against the background of the general pathogenesis of filariasis. We have found

in the recent reports of Rodhain (1953) and Wanson (1953) a complete exposition based on a large personal experience. Their conception is reflected in this paper. *Loa-loa* filariasis has, in common with other types of filariasis, an insidious character of penetration by the organism ; this invasion elicits no local or general reaction over the course of many years although antibodies are formed which may be demonstrated by their deviation of complement. One should distinguish (1) disorders arising from a local reaction to adult filariae ; (2) a second type of local reaction consisting in a lymphatic disorder, suggesting partial obstruction with stasis and oedema, and may have played a role in the production of some of the features we have just reported ; (3) a third type of reaction consisting in allergic cutaneous manifestations (without filariae or with microfilariae *in loco*), revealing themselves as transitory oedemas corresponding to acute attacks of filarial lymphangitis.

Lysis of microfilariae alone cannot be the cause of these phenomena. It is admitted that the presence of the microfilariae has a chronic irritant effect on the lymphatic and connective tissue, but it is still not known whether the lesions result from the direct irritant effect exerted by the microfilariae alone or whether they are conditioned by a previous sensitization of the organism to the microfilariae. Rodhain maintains that in the course of the parasitosis of the human organism by the filariae, the former is sensitized by the adults who produce embryos endowed with antigenic properties. The destruction in large numbers of these embryos provokes the local and general allergic reactions varying in form and intensity according to the number and the specificity of the microfilariae destroyed. In the course of evolution of a filariasis, we see these manifestations produced in various forms. The best known are, without doubt, the filarial lymphagitides, elicited by *Wuchereria bancrofti* and related species (Wucherer, 1868). Their repetition is the cause of the various types of elephantiasis.

As far as *Loa-loa* filariasis is concerned, the best known symptom is Calabar oedema (which in certain individuals recurs with great frequency). One can only say that it bears all the hallmarks of an anaphylactic reaction. There is no fact that proves a direct connexion between the oedema and either a sudden massive destruction of microfilariae or the birth of many embryos. The oedema may occur without detectable filarial embryos in the circulation. It is a typical example of sensitization of the organism by the adult nematode, a sensitization revealed by anaphylactic phenomena whose inception may be manifested under the influence of greatly varied circumstances with differences in intensity dependent upon the parasitosed subjects themselves.

We have shown above that grave complications can supervene without any treatment, and that they can manifest the same symptomatology and the same fulminant evolution as cases in which they appear in the course of or after treatment. This, of course, supposes that the recorded cases to which we have made reference were uncomplicated by the presence of any coexisting disease. Certainly, this applies to the cases of Bonnet (1943), and Cases 1, 2, 3, and 4 of Kivits. On the other hand, in Kivits's second case, the cerebral syndrome appeared 15 days after a local suppuration. Perhaps this is an example of one of the precipitating " circumstances " referred to by Rodhain. It is not impossible that a syphilitic (Bonnet's case, 1943) or trypanosomal (experimental observations of Peruzzi in the monkey, 1928) vascularitis of the central nervous system favours not only the penetration of the microfilariae but also the extension of the allergic reaction to the nervous parenchyma itself.

The encephalitis of *Loa-loa* does not necessarily betray the same fulminant character seen in the cases we have just recalled. It may evolve in bursts ; this phasic development is most marked in the observation by Mme. Bertrand-Fontaine and her collaborators where the deterioration in the patient's condition was interrupted by the treatment.

The encephalitis may be insidious with a psychoneurotic presentation, as in Kenny and Hewitt's (1950) third case, and in the first two observations of these authors, where the removal of an adult filaria had terminated the psychiatric symptoms and eosinophilia.

The cerebral localization of a filariasis can, then, reveal itself simply by vague headaches with depression and apathy or torpor with nothing else to suggest the underlying filarial allergy until the day when an active therapy is instituted. That is what happened in our case. It was the same in the case of Mme. Bertrand-Fontaine and her collaborators and also, with a fatal result, in Case 4 (*M. bancrofti*) of Kenney and Hewitt (1950).

This is all consistent with the view of Rodhain who said of the local and general allergic reactions that they were so characteristic that the therapeutic test, which determines their appearance, indicates a filarial aetiology in cases where the diagnosis is in doubt.

However, the carbamazide used in our case is essentially a microfilaricide or macrofilaricide for *Loa-loa*. The use of this drug in loasis initiates a variety of reactions of variable intensity and

duration affecting the skin, liver, stomach, and joints usually without fever—a reaction assuredly anaphylactic and reacting to antihistamines. These accidents begin on the second day and, as a rule, last for two days. By their rapid lytic action these new drugs can thus bring impressive evidence of the allergic origin of a part of the filarial symptomatology.

Without doubt, the clinical manifestations in all forms of filariasis (*M. loa*, *bancrofti*, and *volvulus*) are irregular and, taking everything into consideration, infrequent, but it is worth while to consider some of them in the light of our present knowledge of allergy.

The changes that we have encountered in the liver, spleen, adrenals, etc., and especially in the central nervous system, are of two types : granulomatous reactions with a variable necrotic component and lesions indicative of an acute, diffuse oedema. The membranes both of the nervous system and the extra-cerebral organs are only involved to the extent that the underlying tissues show granulomatous or oedematous reactions. These two types of reaction are not contemporaneous. The first named are the older and the more striking while the second are terminal, but for the reasons given above we consider both to be connected with the presence of microfilariae, living or lysed. We regard them as evidence of a subacute or chronic allergic affection of the nervous system, depending directly and solely upon the presence of microfilariae and comparable to the relapsing lymphangitides terminating in elephantiasis.

The reactions to microfilariae seen in the cerebral tissue are almost exclusively in the adventitial and glial tissues surrounding the Virchow-Robin space. This is true not only in our case but in the sections from Kivits's case, which, thanks to the kindness of this author, we have been able to re-examine.

Either spontaneously or under the influence of an active chemotherapy, an adventitial reaction or extra-adventitial nodules make their appearance. Then the exudation of plasma or changes in the ground substance characteristic of oedema are seen. It is probable that changes in the walls of the vessels or the adventitial spaces of the brain from other causes (syphilis, trypanosomiasis) play a role, and it is known that all inflammations of the walls of the vessels have an important effect on the blood-tissue barrier, resulting in increased permeability to both antigens and antibodies.

The acute phase of the disease begins with the explosiveness characteristic of other allergic conditions (involvement of the nervous system in serum sickness, in polyarteritis nodosa, in the exanthemata), that is, clinically resembling apoplexy or a cerebral illness with focal symptoms, frequently and fortunately transient, but the histological picture is entirely different from that seen in, for example, post-vaccinial encephalitis. It may, from certain points of view, resemble that seen in polyarteritis nodosa but recalls much more certain experimental encephalomyelitides whose granulomatous character has frequently been stressed (Kabat, Wolf, and Bezer, 1948). Even if the role of this granulomatous reaction in the production of antibodies is debatable, its very constant, if not invariable, presence in certain types of experimental encephalomyelitis, has a significance. This approach indicates, perhaps, a line of treatment to be attempted in the serious accidents of cerebral loasis.

SUMMARY

In filariasis with *Loa-loa*, theoretically, two types of neurological accident may be seen : the first, due to the presence of macrofilariasis, of focal character, the second to the presence of microfilariae, and presenting with subjective mental symptoms and vague neurological features until there is a dramatic complication in the form of hemiplegia or double hemiplegia. On this basic phenomenon, apparently focal and suggesting a thrombosis, there are grafted, in a few cases, other neurological signs, though these are always scanty. This dramatic accident, terminating fatally in a few days, is accompanied by microfilariae in the cerebrospinal fluid, which in other respects shows quite non-specific and minor abnormalities. The neurological complication is part of a generalized disease.

As seen in Kivits's case and in our own, the cerebral complication is the expression of a subacute or chronic encephalitis with a terminal phase representing a fulminant allergic reaction. This terminal phase may supervene spontaneously, though its appearance may be accelerated by a septic incident, by injury to the blood vessels by some other infection, or by the sudden introduction of a large amount of microfilarial antigen consequent upon the initiation of a lytic chemotherapy. The basis of the encephalitis is a diffuse inflammation of the adventitial and vascular apparatus, accompanied by a not inconsiderable glial reaction. This inflammation elicits a nodular reaction with granulomata tending to become necrotic and to be disseminated though with a predilection for certain areas.

In a few areas, the leptomeninges showed local reactions corresponding to those of the vessels, but there was no primary meningitis, ependymitis or infiltration of the choroid plexuses. The peripheral

nerves participate in the disease only to the extent that the perineural lymphatics may be involved.

The electroencephalographic changes may be primarily determined by a pre-existing filarial encephalitis for the changes we have described are not seen in this form in oedema nor in coma.

The question of prevention of such dangerous and insidious neuroallergic reactions is obviously of great importance, especially with the use of heroic doses of antifilarial remedies. It would seem wise in those cases suspected of neural loasis, to attempt a desensitization at the start of treatment either by fractionating the doses of the lysing drug or by combining the drug with antihistaminic substances which appear to act on the tissues taking part in the allergic reaction.

Another approach to treatment might be devised by taking into consideration the granulomatous form of the perivascular reaction which is characteristic of certain types of " allergic vasculitis." It is known that an appropriate dose of A.C.T.H. protects an allergic guinea-pig against the allergic encephalomyelitis which follows injections of heterologous brain substance (Moyer, Jervis, Black, Koprowski, and Cox, 1950) and probably acts at the side of the antigen-antibody reaction. On the other hand, cortisone prevents the development of an experimental encephalomyelitis in the rhesus (Kabat and others, 1947; Morgan, 1947); probably the cortisone suppresses the granulomatous reaction to the antigen at the site of inoculation. There can be no doubt that cortisone is less easily controlled than the antihistamines which have, to a certain extent, an inhibitor effect on experimental encephalomyelitis (Lumsden, 1949), as have also the salicylates (Good, Campbell, and Good, 1949) and mustard gas (Koprowski quoted by Moyer and his collaborators, 1950) but its action is certainly more effective. With cerebral complications as severe as those that we have described, no delay in instituting treatment can be permitted, so when chemotherapy is instituted for the neurological or psychiatric manifestations of filaria, the physician should be prepared, at the first hint of cerebral involvement, to control the allergic reaction by a massive dose of cortisone, possibly combined with antihistaminic substances.

References

Anderson, J. (1924). *Filariasis in British Guiana.* London School of Tropical Medicine Research Memoir Series 5, Memoir 7.

Bertrand-Fontaine, Mme., Schneider, J., Wolfromm, R., and Cagnard, V. (1948). *Bull. Soc. méd. Hôp., Paris*, **64**, 1092.

Bonnet, R. (1943). *Méd. Trop.*, **3**, 273.

Broden, A., and Rodhain, J. (1908). *Névraxe*, **10**, 61.

Brunetière, M. (1913). *Gaz. hebd. Sci. méd. Bordeaux*, **34**, 351.

Chalgren, W. S., and Baker, A. B. (1946). *Arch. Path., Chicago*, **41**, 66.

——, ——(1947). *Medicine*, **26**, 395.

Chambon, M. (1933). *Bull. Soc. Path. exot.*, **26**, 613.

D'Hooghe, M. (1935). *Ann. Soc. belge Méd. trop.*, **15**, 159.

Giaquinto Mira, M. (1934). *Rif. med.*, **50**, 858.

Good, R. A., Campbell, B., and Good, T. A. (1949). *Proc. Soc. exp. Biol., N.Y.*, **72**, 341.

Guyot (1777). Cited by Lorenz, A. *Contribution à l'étude de la filariose.* Thèse de la Faculté de Médecine de Paris, 1890. Ollier-Henry.

Hashimoto, S. (1939). *Trans. Soc. path. Jap.*, **29**, 534. (Cited by Janssens, P. G. 1952.)

Hissette, J. (1932). *Ann. Soc. belge Méd. trop.*, **12**, 433.

Janssens, P. G. (1952). *Ibid.*, **32**, 229.

Kabat, E. A., Wolf, A., and Bezer, A. E. (1947). *J. exp. Med.*, **85**, 117.

——, ——, ——(1948). *Ibid.*, **88**, 417.

Kenney, M., and Hewitt, R. (1950). *Amer. J. trop. Med.*, **30**, 895.

Kivits, M. (1952). *Ann. Soc. belge Méd. trop.*, **32**, 235.

Külz, L. (1908). *Arch. Schiffs-u. Tropenhyg.*, **12**, 547.

Lorenz, A. (1890). *Contribution à l'étude de la filariose.* Thèse de la Faculté de Médecine de Paris. Ollier-Henry.

Lumsden, C. E. (1949). *Brain*, **72**, 198.

Manson, P. (1904). *Maladies des Pays Chauds.* Naud, Paris.

Manson-Bahr, P. (1950). *Manson's Tropical Diseases*, 13th ed. Cassell, London.

Morgan, I. M. (1947). *J. exp. Med.*, **85**, 131.

Moyer, A. W., Jervis, G., Black, J., Koprowski, H., and Cox, H. R. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 387.

Mya, T. (1928). *Indian med. Gaz.*, **63**, 636.

Napier, L. E. (1946). *The Principles and Practice of Tropical Medicine*, p. 679. Macmillan, New York.

Peruzzi, M. (1928). In Final Report of the League of Nations International Commission on Human Trypanosomiasis, pp. 309–313. Geneva.

Pourbaix, E. (1952). *La filariose humaine.* Thèse de l'Institut de Médecine Tropicale, Anvers. Quoted by Janssens, P. G. (1952).

Robles, R. (1919). *Bull. Soc. Path. exot.*, **12**, 442.

Rodhain, J. (1937). *Trans. roy. Soc. trop. Med. Hyg.*, **30**, 501.

——(1953). *Acta trop., Basel*, **10**, 194.

Wail, S. S., Popow, P., and Prjadko, E. (1926). *Virchows Arch. path. Anat.*, **259**, 642.

Wanson, M. (1953). *La vection et la prophylaxie des filarioses humaines.* Veme Congr. Intern. de Méd. Trop. et Paludisme Istanbul, August 28 to September 4, 1953.

Wucherer, O. (1868). *Gaz. med. Bahia*, 3, 97.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 120.

OBSERVATIONS ON THE REACTION TIME TO CUTANEOUS THERMAL STIMULI

BY

P. P. LELE* and D. C. SINCLAIR

From the Department of Anatomy, University of Oxford

The determination of the reaction time to a tactile stimulus is a standard exercise in the practical physiology class, but the student does not always realize just how little weight can be attached to the figures he obtains. Lele, Sinclair, and Weddell (1954) have stressed the great variability of measurements made under different conditions. For example, with a constant force, statistically significant differences occur between corresponding test sites in different subjects and between different test sites in the same subject. Conversely, significant differences in the figures obtained from a given site can be produced by altering the force. The present investigation was undertaken to find out whether a similar variability characterized the reaction times derived from contact thermal stimuli.

PROCEDURE

A copper cylinder with a circular tip 12·5 mm. in diameter was brought to the selected temperature by heating it electrically or by placing it in contact with ice. The temperature of the tip was measured by a thermocouple correct to ±0·25° C., and the temperature of the skin was taken with similar accuracy by a freely suspended thermoelectric junction of copper-constantan wire (Lele, 1954). When the instrument was applied, the stimulator tip made contact with a single strand of 40 s.w.g. copper wire laid on the skin just outside the test area, thereby closing a trigger circuit which started an electronic millisecond timer. A key operated by the subject stopped the timer, from which the reaction time could be read off directly. The results are given in the Tables to the second place of decimals, though the third place was used in calculations.

Five subjects with no experience of sensory tests involving thermal stimuli were used, and on the left hand of each subject one or more test sites were stamped out with ink (Fig. 1). At each session the first step was to allow the skin temperature of the test site to come to equilibrium in a draught-proof room, and the next was to determine the sensory thresholds to cold and warm in the manner described by Lele (1954); as soon as these had been found reaction time measurements were started, the interval between two successive stimuli being varied randomly between two and six minutes. The subject was told that the stimulus might be warm, cool, or thermally neutral, and that he was to press the key as soon as he could tell which it was, simultaneously stating his decision. The order in which different stimulus intensities were applied was made up beforehand, using a table of random numbers, and the stimulator was allowed to remain in position for 20 seconds unless the subject made his decision earlier. Readings

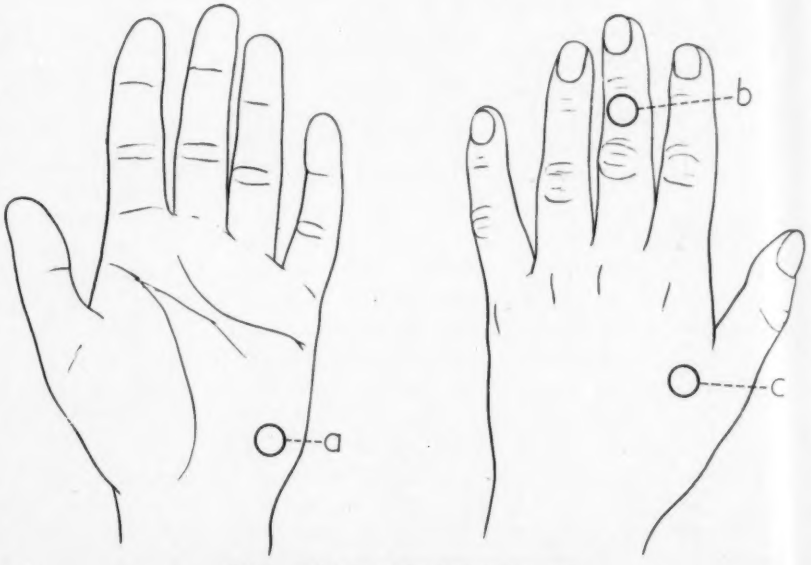


FIG. 1.—Position of test sites on the hand.

* On study leave from the Indian Council of Medical Research.

in which the subject named the stimulus incorrectly were neglected, and the stimulus was repeated later in the series. Similarly, the subject was asked to report immediately if for any reason he felt that he had not responded properly, and the reading in such instances was also discarded. Stimulation was continued until for each stimulus intensity 10 admissible readings of the reaction time were obtained. If the subject felt tired or unable to concentrate, the session was terminated; no comparisons were made between different sets of reaction times unless they were obtained in a random sequence in the same session under identical conditions. Such comparisons were made by applying the t test to the logarithms of the reaction times, the 5% level of probability being selected as significant.

Throughout the investigation stimulus intensities were measured in terms of the observed threshold of the test site, and comparisons between different test areas were made using the appropriate threshold stimulus in each area.

OBSERVATIONS

Site Constant

Reproducibility.—When a constant stimulus was repeatedly applied to the same area, the individual reaction time values showed a scatter round the mean which varied considerably in different subjects. This scatter was greatest the more nearly the stimulus intensity approached the threshold, and became less as the intensity of the stimulus increased. In each of the five subjects an analysis was made of 20 readings derived from a constant stimulus applied to the same site. In none could any statistically significant difference be found between the mean of the first 10 readings and the mean of the second 10. There thus did not appear to be any systematic learning effect which might interfere with the validity of comparisons made at the same sitting. No attempt was made to study any more gradual training changes.

In each of two subjects mean reaction times were obtained for threshold warm and cold stimuli in a given site. On the succeeding day the reaction times were again determined and the results compared (Table I). It was found that statistically significant differences in the reaction times to both warm and cold can occur from one day to another. The times obtained on the second day were not necessarily smaller than those of the first, as might have been expected if the effect were due to learning.

Influence of Stimulus Intensity.—In each subject several different stimulus intensities were applied to a selected site in the course of one session. One of these corresponded to the threshold value for cold and one to the warm threshold figure. Four were arbitrarily chosen suprathreshold stimuli, two being warm and two cold, and the remainder were thermally neutral stimuli inserted as controls. The stimuli were applied in a previously determined random order, and 10 readings for each thermally effective stimulus were obtained. The results are shown in Tables II and III. In each subject the mean reaction time to the strongest stimulus is significantly shorter than the mean reaction time to the weakest stimulus. The mean reaction time to the intermediate stimulus always occupies an intermediate position, and differs significantly from both the others throughout the data relating to cold. With warm stimuli the intermediate stimulus gave results significantly different from the others in seven instances out of 10. Many subjects remarked that the stronger stimuli appeared to have a "sharper onset" than the weaker ones, and that cold stimuli had a more easily recognizable onset than warm. When the mean reaction times were plotted against the logarithms of the intensity of the stimuli an approximately linear relationship was obtained in three of the five subjects for both warm and cold stimuli. No relationship could be worked out in the remaining two subjects because of the considerable differences in the variances of the figures obtained at threshold and suprathreshold levels.

TABLE I

REPRODUCIBILITY

Subject	Day	Site	Skin Temperature (°C.)	Threshold * (°C.)	Mean Reaction Time (sec.) †	Significance of Difference
Warm Stimuli						
W. T.	1	A	32	+2	1·52	—
	2	A	31	+2	1·40	
L. P.	1	B	31	+1·5	0·46	$P<0·05$
	2	B	29	+1·5	0·52	
Cold Stimuli						
W. T.	1	A	32	−2	1·99	$P<0·05$
	2	A	31	−2	2·40	
L. P.	1	B	31	−2·5	0·54	$P<0·05$
	2	B	29	−2·5	0·59	

* Measured from the observed skin temperature. † Each mean is derived from 10 observations.

TABLE II

INFLUENCE OF STIMULUS INTENSITY: WARM STIMULI

Site	Subject	Stimulus Intensity (°C. above Skin Temperature)	Reaction Time in Sec. (Mean of 10 Observations)	Standard Deviation
A	W. T.	2 (threshold)	1·52	±0·23
		4	0·98	±0·07
		18	0·73	±0·03
	J. G.	1 (threshold)	0·74	±0·06
		4	0·65	±0·05
		18	0·54	±0·03
B	R. J.	1 (threshold)	2·14	±0·30
		5	1·35	±0·15
		10	1·27	±0·08
	L. P.	2 (threshold)	0·46	±0·03
		5	0·40	±0·01
		10	0·36	±0·01
C	D. T.	1 (threshold)	0·78	±0·05
		2	0·62	±0·03
		4	0·53	±0·02

TABLE III

INFLUENCE OF STIMULUS INTENSITY: COLD STIMULI

Site	Subject	Stimulus Intensity (°C. below Skin Temperature)	Reaction Time in Sec. (Mean of 10 Observations)	Standard Deviation
A	W. T.	2 (threshold)	1·99	±0·26
		4	0·94	±0·14
		18	0·52	±0·03
	J. G.	1 (threshold)	0·82	±0·05
		4	0·72	±0·03
		18	0·66	±0·03
B	R. J.	3 (threshold)	1·52	±0·16
		5	1·42	±0·18
		10	1·02	±0·06
	L. P.	3 (threshold)	0·54	±0·14
		6	0·44	±0·17
		12	0·36	±0·01
C	D. T.	1 (threshold)	1·21	±0·20
		2	0·71	±0·03
		4	0·63	±0·01

Comparison of Cold and Warm.—In three of the subjects the thresholds for cold and warm were equally spaced on either side of the skin temperature, and it was thought legitimate to attempt to compare the effects of "thermally equivalent" warm and cold stimuli in these subjects, i.e., pairs of stimuli whose temperature was equidistant from the skin temperature. The results of this comparison are shown in Table IV. In one subject no statistically significant differences could be demonstrated between cold and warm reaction times, but in the other two the warm times were invariably significantly smaller than the cold times.

Site Variable

Comparison of Different Sites in Same Subject.—In three subjects the finger site B was compared with the hypothenar site A, using threshold stimuli for each site. Table V shows a tendency for the thresholds for both cold and warm stimuli to be higher on the finger, but no general trend among the reaction times. The only significant difference was that in subject W.T. threshold cold stimuli gave longer times from the finger than from the hypothenar eminence.

Comparison of Similar Sites in Different Subjects.—Wide differences were sometimes observed. A threshold warm stimulus applied to the finger test site produced in one subject a mean reaction time of 0·46 seconds, and in another a mean time of 2·14 seconds (Table II). Similarly, the response to a threshold cold stimulus on the hypothenar site took 0·82 seconds in one subject and 1·99 in another (Table III). Both these differences are statistically significant.

DISCUSSION

Evidently the reaction time to touch is not unique in its capacity to vary grossly with the experimental conditions, for we have shown that alterations in the intensity of the stimulus can cause statistically significant alterations in the reaction times to both cold and warm stimuli. We have also found that, when comparisons are based on threshold stimu-

TABLE IV

COMPARISON OF REACTION TIMES TO COLD AND WARM

Subject	Stimulus Intensity *		Reaction Time (Mean of 10 Values in Seconds)		Significance of Difference
			Warm	Cold	
J. G.	+1	−1	0·74	0·82	$p<0·01$
	+4	−4	0·68	0·72	$p<0·01$
	+18	−18	0·54	0·66	$p<0·001$
W. T.	+2	−2	1·52	1·99	—
	+4	−4	0·98	0·94	—
	+18	−18	0·73	0·52	—
D. T.	+1	−1	0·78	1·21	$p<0·02$
	+2	−2	0·62	0·71	$p<0·05$
	+4	−4	0·53	0·63	$p<0·01$

* The stimulus intensity is measured in °C. from the skin temperature.

TABLE V

COMPARISON OF REACTION TIMES DERIVED FROM DIFFERENT SITES

Subject	Site A		Site B	
	Threshold	Reaction Time	Threshold	Reaction Time
Warm Stimuli				
R. J. ..	+3	2·20	+1	2·14
W. T. ..	+2	1·52	+4	1·60
L. P. ..	+1	0·51	+2	0·46
Cold Stimuli				
R. J. ..	−1	1·48	−3	1·52
W. T. ..	−2	1·99	−4	3·32
L. P. ..	−2	0·59	−3	0·54

The thresholds are given in °C. above or below skin temperature; the reaction times are the mean of 10 readings in seconds.

lation, the reaction time at a given site need not be constant from day to day, that the reaction time to stimulation of the corresponding site in different individuals can vary significantly, and that the reaction times to cold stimuli can vary significantly from one test site to another in the same subject. The use of threshold stimuli for such comparisons requires some comment.

When stimuli of gradually increasing temperature are applied to the skin, they are at first appreciated as cold, then thermally neutral, then warm, and finally painful. At either end of the thermally neutral zone lie the thresholds for warm and cold. Now Lele (1954) has shown that the position of this neutral zone on the thermometric scale varies fairly closely with the skin temperature of the test area, which may fluctuate from time to time and from place to place. Cold and warm thresholds, measured in terms of a fixed temperature scale, are thus extremely labile, and a stimulus of a given temperature applied to a given area might be perceived as cold, neutral or warm according to the local condition of the skin. On the other hand, thresholds measured in terms of the skin temperature remain more or less constant over a wide range of temperatures (Lele, 1954). Now at threshold intensity we may conceive that the obstacles lying between the stimulus and the end-organs which it is to activate have been overcome, and enough energy has arrived at the nerve terminals to arouse a propagated disturbance of a kind which will be interpreted on arrival at the brain as a thermal sensation. Further increases in the amount of energy arriving will be interpreted as increases in the intensity of the sensation, and the threshold is thus the logical zero point for any scale of measurement of intensity of either sensation or stimulus. Exactly the same considerations apply to stimuli involving other modalities. It is probable that the tactile threshold, for example, varies with the local conditions, and so we are not justified in comparing results obtained in different areas or at different times by the use of stimuli measured in absolute and not in relative terms. Little attention has been paid to such matters in the past, and perhaps some of the numerous discrepancies in work on skin sensation stem from this cause.

In the present investigation the cold and warm thresholds were usually spaced equidistant from the skin temperature, and measurements of stimulus intensity are given in degrees measured from the skin temperature. Where the thresholds are equivalent we may tentatively assume that suprathreshold stimuli equidistant from the thresholds are also equivalent, and so compare the reaction times to cold and warm. Such evidence as we have suggests that under these experimental conditions there is a tendency for the reaction time to a warm stimulus to be shorter than the reaction time to a cold stimulus of equivalent intensity. This is in contrast to the findings of Jenkins (1938) under different experimental conditions.

The variability of the reaction time to thermal stimuli has not received much attention in the literature. Bazett, McGlone, Williams, and Lufkin (1932) used reaction time measurements to determine the depth from the skin surface of the receptors for warm and cold, but the assumptions made in their calculations must now be considered unwarranted. In 1937 Hardy and Oppel noticed that the threshold for warm depends on the area of the stimulus, and in 1938 Jenkins found that the reaction time to warm is affected by stimulator size, though curiously he did not observe any such effect with cold stimuli. Lele (1954) has shown that both warm and cold thresholds vary according to stimulus size, and this may be correlated with the work of Wright (1951) who found that the reaction time to a radiant heat stimulus varies with the size of the stimulus. Wright (1951) also showed that for radiant heat the reaction time depends on the intensity of the stimulus, and both these findings have since been confirmed by Lele, Weddell, and Williams, (1954).

Perhaps the most important implication of our present extension of these investigations is that thermal reaction times are so dependent upon experimental conditions as to make it unjustifiable to use them to allocate specific conduction velocities to thermal sensations. The same has already been demonstrated for touch sensibility (Lele, Sinclair, and Weddell, 1954) and is probably also true for painful sensations. Reaction time measurements have in the past provided one basis for the idea that specific sensory modalities are carried in specific ranges of fibre sizes to the central nervous system, and that the " pain fibre " is distinguishable from the " touch fibre " by its size. It is true that the thermal reaction times we have reported in this paper are in general somewhat longer than the touch reaction times we reported elsewhere (Lele, Sinclair, and Weddell, 1954), but this cannot be taken to mean that thermal sensations are in general carried in smaller and more slowly conducting sensory fibres. The reaction time is the sum of many smaller times ; the time taken for initiating conduction, for conduction itself, for perception and judgment, for synaptic crossings, and for traversing the efferent pathway (Michon, 1939; Monjé, 1934). Only if it is assumed that the conduction time alone is variable can any estimate of the conduction velocity be made, and this

assumption we have no right to make. Indeed, for touch stimuli it has been shown clearly to be false (Lele, Sinclair, and Weddell, 1954).

SUMMARY

Reaction times in response to warm and cold contact stimuli can be shown to vary according to the intensity of the stimulus.

It is desirable, and for thermal stimuli essential, to express stimulus intensities by measuring them from the threshold intensity and not from an absolute zero. Only in this way can legitimate comparisons between different areas, different sessions, and different subjects be drawn.

Using threshold warm and cold stimuli it can be shown that thermal reaction times may vary from day to day, from site to site, and from subject to subject.

It is not legitimate to use thermal reaction times to derive figures purporting to represent conduction velocities for thermal sensations.

We should like to thank the volunteers who took part in this investigation, and the Rockefeller Foundation for the grant which made it possible.

REFERENCES

Bazett, H. C., McGlone, B., Williams, R. G., and Lufkin, H. M. (1932). *Arch. Neurol. Psychiat., Chicago*, **27**, 489.
Hardy, J. D., and Oppel, T. W. (1937). *J. clin. Invest.*, **16**, 533.
Jenkins, W. L. (1938). *J. exp. Psychol.*, **22**, 178.
Lele, P. P. (1954). *J. Physiol., Lond.*, **126**, 191.
——, Sinclair, D. C., and Weddell, G. (1954). *Ibid.*, **123**, 187.
——, Weddell, G., and Williams, C. M., (1954). *Ibid.*, **126**, 206.
Michon, P. (1939). *Le Temps de Réaction.* Masson, Paris.
Monjé, M. (1934). *Z. Biol.*, **95**, 467.
Wright, G. H. (1951). *J. Physiol., Lond.*, **112**, 344.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 125.

CHRONIC PROLIFERATIVE OSTEITIS OF THE SKULL

BY

J. E. M. DUTTON and G. L. ALEXANDER

From the Department of Neurological Surgery, Frenchay Hospital, Bristol

Three cases of this condition have come to our notice in recent years; in two of them the process was related to a chronic extradural abscess. Our purpose in this report is to describe our experience with these cases and to indicate the lessons which we believe may be learnt from them.

Case Reports

Case 1.—This patient was a man of 42 years. Twenty-one years before, a left posterior frontal abscess had appeared spontaneously under the scalp. The abscess ruptured after three weeks, and thereafter a chronic sinus discharged intermittently. Local surgical exploration was undertaken on three occasions at long intervals, at the latest of which, bone an inch thick was chiselled away, releasing some extradural pus. The sinus continued to discharge, and the patient noticed that coughing and straining on occasion caused as much as an ounce of pus to escape from the sinus. (Ambroise Paré described this feature of "open" extradural abscess.)

He had no symptoms except a mild local headache each time the sinus was about to discharge.

In the period since the appearance of the cranial infection an ischiorectal abscess, and later a Brodie's abscess of the humerus, had been successfully treated.

On examination there were no neurological abnormalities. The patient was pale and rather "toxic" looking. A radiograph of the skull (Fig. 1) showed changes in the bone. The blood Wassermann and Kahn reactions were negative.

FIG. 1.—Appearance of the skull in Case 1. The thickening of calvarium extended only to the midline.

At operation in February, 1951, the sinus-track in the bone was found to be about 5 mm. in diameter, with rounded margins. A rectangular block of calvarium about 25 mm. thick and 9 cm. square was removed, exposing almost the whole of a chronic extradural abscess. In making the saw-cuts a bevelling of about 45° was arranged so as to minimize "dead-space" on closure. The bone was dense, fairly hard and there was no indication of diploe.

The extradural abscess extended a short distance inferiorly towards the supraorbital ridge, and bone was nibbled away to expose fully the abscess cavity. The wound was closed in two layers, with three gutta-percha tissue drains which were later shortened, and removed on the eighth day. Systemic penicillin and sulphamezathine were given and healing was satisfactory.

Two organisms were recovered on culture: *Staph. albus* and β-*haemolytic streptococcus*, both sensitive to penicillin and streptomycin, but resistant to sulphonamides. It may be significant that sulphonamides had been used in this man's infection of the humerus and peri-rectal tissues.

Eight months later the bone flap, which had been stored sterile, was re-inserted, provision being made for the instillation of penicillin. Two months later clear, yellow, sterile fluid was aspirated from under the scalp flap. There was no pyrexia.

There has been no sign of recurrence of infection anywhere in the three years to date, although we had initially some anxiety as to how the tissues would receive this substantial block of dead bone.

Case 2.—This was a woman aged 33 years. She had a 31 years' history of recurrent cranial infection, beginning with a scalp abscess near the vertex, following pneumonia at the age of 2 years. The abscess was incised and later healed. The family then moved overseas. At the age of 10 years this patient was assailed by a serious malady with marked pyrexia, rigidity of the limbs, and unconsciousness; it was not thought that she would recover. Lumbar puncture did not confirm the diagnosis of "meningitis". (Details of this illness are not procurable.) She recovered, contrary to all expectations.

Some months later an abscess of the scalp began to discharge, and continued to do so intermittently over the years, each episode of discharge being preceded by headache at the vertex. Horizontal diplopia was noted on one such occasion.

FIG. 2.—Appearance of the skull in Case 2.

FIG. 3.—Endocranial aspect of the bone flap in Case 2.

The sinus was opened and curetted when the patient was 18 years old.

Twelve years ago she came under neurosurgical care in this country, with a discharging sinus above the left ear. Papilloedema was present. A burr-hole intended for ventriculography released 55 ml. of extradural pus. The cavity was drained for six weeks, and all three foci of drainage soon closed.

All was well for five years, then the parieto-occipital sinus again opened and discharged for months at a time, at long intervals. Local throbbing headache preceded each breakdown.

On examination she looked well. There was a small sinus near the midline and behind the vertex which had been discharging green pus continuously for seven months (dressed thrice daily). The scalp was reddened and oedematous, but not tender, for some 4 cm. wide of the sinus all round. Nearby posteriorly were some operation scars where the scalp was thin and fixed. The regional lymph glands were not palpable. There was no pyrexia nor any abnormal neurological signs. The blood Wassermann and Kahn reactions were negative. The *x*-ray appearance is shown in Fig. 2.

At operation in October, 1953, block resection of diseased calvarium over an area of 15 by 18 cm. revealed an extensive indolent extradural abscess, with shaggy granulations but little pus. The margins of the craniectomy were cut with a pronounced bevel, as in Case 1. The endocranial aspect of the bone-flap was extremely irregular but not eroded. The inner table bore incrustations and irregularities, but its surface was intact (Fig. 3). The dura mater was extremely thickened and semi-rigid, except peripherally beyond the sharply delimited abscess.

The craniectomy extended to the midline superiorly, and bleeding from the sagittal sinus was controlled with gelatine foam later removed lest it form a nidus for infection. Sulphanilamide powder was insufflated and the scalp closed with one layer of sutures. Two guttapercha tissue drains and a tube for instillation of penicillin were provided ; these were removed after two days. Penicillin was instilled daily, 50,000 to 100,000 units at a time, for five days. Aureomycin was given thereafter for several days. Healing was rapid, but a small amount of serous discharge persisted at the old unhealthy sinus area. At operation the scalp here was found to be thin and devitalized over an area too extensive to permit of excision and suture.

The cultures from a deep field at operation were sterile, and no organisms were seen in films. Later cultures from the persisting localized sinus grew *Staph. pyogenes*, universally sensitive.

We had contemplated re-insertion of the sterile stored bone flap, which weighed 376 g., but that was impracticable because of the risk presented by the thin area of scalp. Moreover, as pointed out by King (1937), in the more acute osteitis regeneration of bone after craniectomy is to be anticipated. Incidentally, experience has shown that the misfortune of operative infection around bone grafts may ultimately promote abundant union.

Six months after craniectomy the thin area of scalp was widely resected and a large sliding graft was swung over from the right side.* We saw no evidence of recurrent suppuration wide of the small sinus at this second operation. We believe it would be bad surgery to insert the bone flap now in this wound, even were it desirable.

Recent *x*-ray films, taken a year after the craniectomy, show several foci of re-ossification at dural level. The scalp is in excellent condition.

Case 3.—The patient, a man aged 32 years, sustained a non-concussional blow with a cricket ball on the right temple when he was 9 years old. He suffered from headache for a short time afterwards, but attended school without interruption. Two weeks later he had

* We wish to acknowledge gratefully the assistance of Mr. G. M. FitzGibbon and Mr. Routledge of this hospital in planning the incisions for this plastic repair.

FIG. 4.—Appearance of the skull in Case 3. Hyperostosis is external; note the even contour of the inner table. *By courtesy of Dr. A. R. Thomas.*

FIG. 5.—Appearance at operation in Case 3. The burr-hole lies posteriorly.

a sudden "black-out", but no convulsion and no incontinence. A similar brief attack followed three days later. The patient was admitted to the local hospital where he had an operation on the following day. (No details now procurable.) He remained in hospital for nine months, and at intervals eight operations were performed through short incisions. Small sequestra were extruded spontaneously from time to time. He then attended as an out-patient for four years on account of a discharging sinus at the right temple. During this time he had recurrent headaches but no febrile symptoms.

He remained well for 14 years, then had a sudden attack of unconsciousness without overt epileptic phenomena. Thereafter, he had recurrent right frontal headaches for a few days at a time. There was no vomiting or pyrexia, and no neurological symptoms.

Nine weeks before he came under our care he developed a red, tender, hot swelling near the midline of the forehead, which was incised after a short course of penicillin; no pus or organisms were found. He was febrile at the onset. The wound quickly healed and the headaches ceased.

Examination showed a fit-looking man. There were eight small scars in the temporal region and near the midline of the forehead; the skin was thin and adherent to the bone at some of the scars. The thickening of the frontal bone terminated rather abruptly at about the level of the coronal suture, where a "step" was palpable. This was in contrast to the foregoing cases, where no indication of the limits of hyperostosis was detectable by palpation. There were no abnormal neurological findings. The blood Wassermann reaction was negative, and the cerebrospinal fluid was normal at a pressure of 150 mm. The *x*-ray appearances are shown in Fig. 4; the frontal air sinuses appeared healthy.

At operation in December, 1953, an intertemporal incision was chosen to provide a large frontal scalp flap. The skull presented a diffuse right frontal and median bossing, and the surface was extensively roughened and pitted, the fibrous tissue of the thick periosteum dipping down into these pits (Fig. 5). Five burr-holes made in the right temporal region and three large drill holes near the frontal midline yielded no pus; the visible dura was normal. The wound was closed without drainage. Mild oedema of the scalp persisted for some days, and sterile fluid accumulating under it was aspirated on two occasions. Penicillin was administered during operation and subsequently.

In the year since operation this patient has had two attacks of headache, each associated with coryza. These have cleared with symptoms suggesting the resolution of an obstruction in one frontal sinus.

Discussion

This hyperostotic reaction of the calvarium to chronic pyogenic infection must be somewhat rare. It is, however, possible that conditions of the skull akin to this may appear sporadically in the future where intensive systemic treatment of acute osteitis of the skull with penicillin has just failed to stamp out the infection completely. In this connexion the long clinical remissions in the cases described may be pertinent. And indeed time may perhaps show that we have been less successful with these cases than we believe.

The only relevant paper which we have found in the literature is one by Maxwell (1946) describing chronic proliferative osteitis affecting the base of the skull and adjacent calvarium following frontal sinusitis treated by local operations. Follow-up is not recorded.

It is to be noted that the hyperostosis extended well beyond the limits of the extradural abscesses and that the bone showed no gross evidence of infection. The extent of the hyperostosis in each case corresponded to a suture line at one or more of its boundaries. The term osteitis applied to this condition might therefore be questioned, but it seems to us convenient. The hyperostosis appeared to be

a reaction of healthy bone to adjacent chronic infection. The surface of bone contiguous with the focus of suppuration in each case showed irregularities but no necrosis or hint of sequestration at an earlier stage. Sequestra were discharged in the initial subacute phase in Case 3, and there was undoubtedly a grumbling osteitis of the outer table. In that particular case we have no accurate information as to the presence of a septic cut or abrasion after the injury, but the infection probably came from without.

In two patients the cranial infection appeared in childhood, but the similar findings in Case 1 preclude a deduction that infection arising during the growth period is a factor in the pathology.

Acute infection in bone is associated with hyperaemia and leads to osteolysis. Chronic infection causes osteosclerosis, and probably surrounding scar formation induces a relatively anoxaemic state locally in the affected bone tissue. Even so, the extent of the hyperostosis beyond the obvious focus in the cases described is a feature of interest. Incidentally, a good case has been made out for chronic local hypoxia as the basis for deposition of calcium in the cerebral cortex by Alexander and Woodhall (1943) and the same circumstance probably accounts for the cortical calcifications in the Sturge-Weber anomaly (personal observations in progress).

The headache in the first two cases was probably of dural origin. In Case 3 it was described by the patient in terms which suggested the pain of periostitis ; it was relieved by local surgery in his earlier years, and our fruitless exploration involving extensive stripping of periostium was promptly effective. The behaviour of this man's headache in years to come will be of interest.

Infection apparently did not spread transdurally in any case. Our interpretation of the scanty information about the serious malady in childhood in Case 2 is that the patient was in peril from the effects of brain-stem compression occasioned by a substantial extradural abscess.

Regarding treatment, it is obvious that the principles accepted in the surgery of acute osteitis of the skull must be applied to these chronic infections. Small local drainages cannot cure a chronic extradural abscess. The ability of cocci to remain dormant for long periods in avascular tissue is notorious. We found no pus in Case 3 and therefore did not perform craniectomy.

We wish to express our indebtedness to the laboratory staff, and to Mr. Banham, of the photographic department of Frenchay Hospital, for their help with the investigations and records.

References

Alexander, L., and Woodhall, B. (1943). *J. Neuropath.*, **2**, 1.
King, J. E. J. (1937). *Surgery*, **1**, 401.
Maxwell, J. H. (1946). *Ann. Otol., St. Louis*, **55**, 719.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 129.

THE ASSOCIATION OF DEMENTIA WITH RADIOLOGICALLY DEMONSTRATED CEREBRAL ATROPHY

BY

R. H. GOSLING

From the National Hospital for Nervous Diseases, Queen Square, London

Dementia beginning in late middle life raises many medical problems. It is caused by a variety of pathological processes which even after post-mortem examination of the brain may remain obscure (McMenemey, 1941 ; Rothschild, 1941). If some cerebral lesion, such as atrophy or tumour, can be detected during life the diagnosis can be put on a firmer footing, and it is to this end that cases presenting with dementia are often investigated by means of a lumbar air encephalogram (A.E.G.). If a tumour is revealed by an A.E.G. the problem is considered settled. If cerebral atrophy is demonstrated then this is assumed to account for the dementia (Chodoff, Simon, and Freeman, 1948). But we are not always so successful. Sometimes no lesion is revealed by an A.E.G. and the dementia remains unexplained. On the other hand, gross generalized cerebral atrophy is occasionally found in a patient without the slightest impairment of mental function, but in whom an A.E.G. was thought necessary for some other reason.

The purpose of this paper is to determine the value of the A.E.G. in investigating the dementias of late middle life, and for this the experience of routine examination in a neurological hospital has been surveyed. Exact pathological diagnosis, though desirable, was not available in this material, and so the problem has been restricted to cases of dementia after the age of 45 for which no definite cause, such as tumour, could be found.

Investigation

Abstracts were made of the case notes of all patients coming to the National Hospital for Nervous Diseases, Queen Square, London, between April, 1949, and March, 1953, who showed dementia beginning after the age of 45 and who had had an A.E.G. done. Cases of the following conditions were excluded : Huntington's chorea, other degenerative conditions with systemic involvement of the central nervous system, cerebral tumour, head injury, and arteriosclerotic dementia that was beyond dispute, i.e., dementia dating from a cerebrovascular accident. We were thus left with a collection of certain conditions characterized by the onset of dementia after the age of 45. Presumably it included senile, Alzheimer's, Pick's, and some arteriosclerotic dementias, together with a few conditions that were misdiagnosed or in which the diagnosis was left in doubt. There were 68 such cases (Table I). Because of the indefinite composition of the case material throughout this paper the data are presented in five-year age groups.

TABLE I
INCIDENCE OF CEREBRAL ATROPHY IN CASES OF DEMENTIA

Age	No. of Cases of Dementia Examined by A.E.G.	Dementia with Atrophy		Dementia without Atrophy	
		No.	%	No.	%
45–	7	6	86	1	14
50–	18	16	89	2	11
55–	22	19	86	3	14
60–	16	12	75	4	25
65	5	5	100	0	0
Total	68	58	85	10	15

The dementia was judged clinically. From a perusal of the records it was rated as slight, moderate, or marked, but it should be remembered that these records were prepared by a number of house officers with no particular interest in the delineation of dementia, and that the rating of the records was done retrospectively by the author. Those cases showing only a falling off of memory, or only mild, unwonted emotional lability, or only an intellectual impairment that was so indefinite that the help of a psychologist was sought, were rated as " slight ". Those cases showing an almost complete dissolution of the personality, or such disorientation that constant nursing care was required, were rated as " marked ". The cases falling between these extremes were rated as " moderately " demented. Such a rating may be thought invalid. Certainly demented people show a variety of early symptoms

and may show a greater loss in some respects than others. Nevertheless, there is usually an overall impairment of mental function which gradually increases, and so a three-point scale may have some justification.

Likewise cerebral atrophy may declare itself in the A.E.G. in a variety of ways; there may be generalized or localized enlargement of sulci, dilatation of the ventricular system in part or in whole, or any combination of these. Furthermore, if one abnormality is demonstrated, a search for other defects is often not made; thus if the lateral ventricles are clearly dilated a special effort to delineate the cortical sulci may not be made, or if enlarged sulci are demonstrated in one part of the cortex a careful survey of other parts of the cortex will not usually be carried out. As there is little tendency towards global atrophy apparent in the A.E.G.s, to rate the degree of atrophy is impossible; in the Tables, therefore, it is stated as either present or absent. Strictly speaking the radiologist concerned reported that atrophy was or was not demonstrated, and in the latter category fell a number of cases in which the examination did not fully satisfy him. An attempt to correlate various features of the A.E.G. with the presence or absence of dementia is made later.

Table I shows that of the 68 cases of dementia 85% showed cerebral atrophy in the A.E.G. and 15% did not. The question was raised whether the proportion of cases showing cerebral atrophy would be changed if stricter criteria were used in selecting the cases. Perhaps, for example, most of the cases showing dementia without radiological atrophy were arteriopathic. These 68 cases were therefore reviewed again and all cases were rejected which, according to Rothschild (1941), were likely to have predominant cerebral arteriosclerosis, i.e., with any of the following: prominent anxiety, fluctuating course, conspicuous preservation of insight, attacks of giddiness, a diastolic blood pressure greater than 120 mm. Hg, or associated Parkinsonism or coronary artery disease. Eighteen cases were rejected in this way, but of the remainder the proportion that showed cerebral atrophy was unaltered, namely 84% (Table II). This suggests either that the association of dementia with cerebral atrophy is independent of whether the cause is arteriosclerosis or some other process, or that Rothschild's criteria are unsound.

In the original 68 cases there were 10 that showed dementia but no atrophy and a closer inspection of them may be worth while. In the first place, slight dementia was significantly more frequent amongst these 10 cases than amongst the 58 cases that showed atrophy. Thus, out of 27 cases with a slight degree of dementia only 19 (70%) showed cerebral atrophy, whereas from among 41 cases with moderate or marked dementia 39 (95%) showed atrophy; this difference is highly significant ($\chi^2 = 10{\cdot}05$; $P < 0{\cdot}01$). Follow-up by letter at least one year after discharge from hospital showed that, as discussed later, there are reasons to doubt the accuracy of the diagnosis of dementia in these 10 cases in that out of six successfully traced only one had deteriorated. In the second place, a new scrutiny of the films revealed that of the 10 cases there was only one indubitably normal A.E.G.; in three the examination, though normal so far as it went, was inadequate to exclude some degree of atrophy; and in six there were borderline abnormalities (Table III). Thus only one case was known for certain to have demented progressively despite an almost normal A.E.G.

TABLE II

INCIDENCE OF CEREBRAL ATROPHY IN CASES OF DEMENTIA AFTER EXCLUDING MOST ARTERIOPATHIES

Age	No. of Cases of Dementia Examined by A.E.G. after Excluding Most Arteriopathies	No. of Cases of Dementia with Atrophy	No. of Cases of Dementia without Atrophy
45–	5	4	1
50–	12	11	1
55–	18	16	2
60–	11	7	4
65	4	4	0
Total	50	42 (84%)	8 (16%)

TABLE III

FOLLOW-UP OF 10 CASES ORIGINALLY REPORTED AS DEMENTED WITHOUT EVIDENCE OF CEREBRAL ATROPHY

Rescrutinized A.E.G.	Length of Follow-up (years)	Mental State at Follow-up
Normal	3	Well
,, but incomplete	4	Well
,, ,, ,,	1	Well
,, ,, ,,	—	—
Sulci enlarged to 5 mm.	1/12	Died demented
,, ,, ,,	—	—
,, ,, ,,	—	—
,, ,, ,,	—	—
Ventricles slightly enlarged	2	Died but not demented
Sulci enlarged more than 5 mm.	1	Well

We must next consider how often cerebral atrophy is found when there is no evidence of dementia. During the same period and in the same age group a number of cases of cerebral atrophy came to light through A.E.G.s performed in the investigation of conditions other than dementia, usually cases suspected of having a cerebral tumour. There were 41 such cases, but this number was reduced to 24

if those cases were excluded in which a definite diagnosis could be made to account for the atrophy, viz., disseminated sclerosis, thrombosis of the common carotid artery, cerebrovascular accident, neurosyphilis, infiltrating glioma, and infantile hemiplegia. The majority of the 24 were finally labelled " epilepsy of late onset ", fits being significantly more common in these cases than in those with dementia in addition to the atrophy ($\chi^2 = 18{\cdot}46$; $P < 0{\cdot}001$—see Table IV). But in the absence of a follow-up study the exact contents of this group remain indefinite.

TABLE IV

INCIDENCE OF FITS IN CASES OF CEREBRAL ATROPHY WITH AND WITHOUT DEMENTIA

Age	No. of Cases of Atrophy with Dementia		No. of Cases of Atrophy without Dementia	
	Fits	No Fits	Fits	No Fits
45–	3	3	6	1
50–	4	12	4	0
55–	5	14	5	2
60–	3	9	4	1
65	1	4	0	1
Totals	16	42	19	5
	58		24	

It might seem that the discovery of 24 cases of cerebral atrophy, when none was suspected from the mental state of the patient, diminishes the value of the A.E.G. But it should be remembered that these 24 cases came to light in a very large number of A.E.G.s performed for a variety of reasons, actually 213, of which 189 showed some lesion other than atrophy, or were normal (Table V). That is, of 213 A.E.G.s performed for various reasons in cases without any dementia only 24, or 11%, showed cerebral atrophy that could not be explained.

TABLE V

INCIDENCE OF CEREBRAL ATROPHY IN A.E.G.s PERFORMED FOR REASONS OTHER THAN DEMENTIA

Age	No. of Cases without Dementia but with Atrophy	No. of Cases without Dementia or Atrophy	Total
45–	7	60	67
50–	6	55	61
55–	5	32	37
60–	5	29	34
65	1	13	14
Total	24 (11%)	189	213

Criteria of Usefulness of the A.E.G.

The same data can also be used to determine what features of the A.E.G. are most useful in predicting the presence of dementia, and how well they do it.

Scrutiny of the A.E.G. films was kindly undertaken by Dr. G. Thomson, who knew that cerebral atrophy was the subject under investigation but who knew nothing of the individual cases. Films of the following cases were assembled in random order : 54 cases of dementia with atrophy (the films of the other four could not be traced), 10 cases of dementia without atrophy and 24 cases of atrophy without dementia, making 88 in all (Tables I and V). Each set of films consisted of the six standard positions (Lysholm, 1935) and was examined for the following six features (Fig. 1), and the results noted down on the back of the clinical abstract :

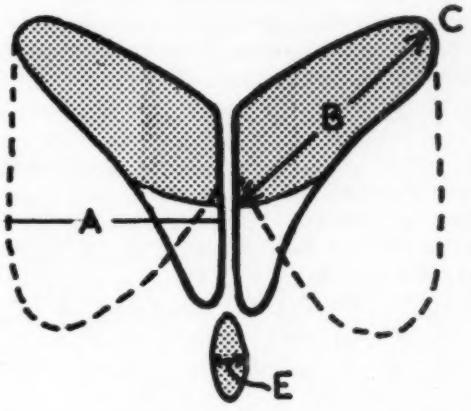


FIG. 1

A = Width of anterior horn of lateral ventricle.
B = Diagonal diameter of body of lateral ventricle.
C = Upper angle of lateral ventricle.
D = General configuration of lateral ventricle.
E = Transverse diameter of third ventricle.
F = Width of cortical sulci.

The upper limits of normal for A and B were taken arbitrarily as 2·6 cm. and for E as 0·8 cm. Evans (1942) found in 53 normal adults and children no case in which the transverse diameter of both anterior horns together was greater than 4·4 cm. Our upper limit for A would give a corresponding figure of 5·2 cm., and so we are not likely to have inflated our abnormal group with borderline normals. Davies and Falconer (1943) measured the diagonal width of the body of the lateral ventricles in 50 cases thought to be normal and found none greater than 2·2 cm. Thus our upper limit for B is also conservative. Davidoff and Dyke (1951) found the transverse diameter of the third ventricle not to exceed 0·8 cm. in 150 normal subjects. The upper angle C was judged by the eye as normal or widened. Cortical sulci were measured whenever possible and were rated as normal (up to 0·2 cm.), slightly enlarged (0·2 to 0·5 cm.), and greatly enlarged (over 0·5 cm.). Davidoff and Dyke (1951) found normal sulci rarely greater than 0·3 cm. These norms, however, leave out of account the factor of age.

Heinrich (1939), in examining the A.E.G.s of 100 normal individuals, found a progressive enlargement of the ventricles and subarachnoid space with age which was particularly marked over the age of 60 but he gives no figures. Furthermore, all these features could not be inspected in every case because of inadequate filling with air, the commonest omission being thorough visualization of the sulci.

The cases were sorted into three groups: one, those showing no dementia, numbering 24; two, those showing moderate or marked dementia, numbering 39; the remainder, consisting of 25 cases of slight dementia, were ignored, as they included a number in which the dementia was indefinite or so slowly progressive that it seemed to fall outside the usual clinical categories. The first two groups were then inspected for features of the A.E.G. that distinguished them most clearly. Only 16 of the first group and 28 of the second allowed adequate examination of both cortex and ventricles. The two groups were best distinguished by the presence of any of the following: (1) Cortical sulci greater than 0·5 cm., (2) air trapped in the insular region of the cortex, (3) enlargement of one or both of the lateral ventricles particularly marked in the region of the trigone, whether or not they were enlarged elsewhere.

Using these criteria 12 out of 16 cases without dementia were correctly classified and 23 out of 28 cases with dementia (Table VI). No other features were useful in distinguishing the two groups. The validity of these criteria must be tested on another collection of demented and non-demented cases.

TABLE VI

DERIVATION AND VALIDATION OF A.E.G. CRITERIA

Experiment	Group	No. of Cases	Correctly Sorted by Criteria	Wrongly Sorted by Criteria	Misclassified (%)
Derivation	Cases without dementia	16	12	4	25
	Cases with dementia	28	23	5	18
Validation	Cases without dementia	12	9	3	25
	Cases with dementia	5	4	1	20

Such a collection, though small in number, is provided by the 25 cases of slight dementia that were ignored. As has been seen, some of the patients rated as slightly demented were found on follow-up to show no deterioration of their mental state. In the age groups under review most dementias are progressive, and so, while not conclusive evidence, a report that the patient was improved or had not deteriorated in his mental capacity at least a year after leaving hospital may be considered to indicate that the original classification as "slightly demented" was mistaken. In this collection, therefore, follow-up provides us with a group of cases of undoubted dementia, and a group in which dementia is very unlikely. Our A.E.G. criteria may then be validated against these two groups.

Of the 25 cases only 22 had adequate A.E.G.s available. These 22 cases were followed up by mail at least a year after they had left hospital, and 17 replies were received; from them it appeared that five were demented and 12 were in fact not demented. These 17 cases were arranged according to the A.E.G. criteria and the correctness of the prediction of dementia determined (Table VI). As will be seen, the prediction was correct in about three cases out of four. Validation of these criteria is desirable on a much larger series of cases.

Discussion

This paper contributes little to fundamental knowledge of cerebral atrophy and dementia; rather is it a retrospective survey of the results of routine investigation. Attempts have been made in the past to correlate ventricular size at necropsy with the pathological changes in the cortex characteristic of senile and presenile dementia (Morel and Wildi, 1953), but I am not aware of any study consisting of more than a few isolated examples in which evidence in the A.E.G. of cerebral atrophy is related to the presence or absence of dementia. The results here presented have doubtless been suspected by most clinicians for some time, and in so far as they indicate clearly the usefulness of the A.E.G. in cases presenting with dementia they may modify routine practice. A different selection of cases may then be investigated and it is unlikely that what has been found to hold true in the present group will be found to apply exactly to a new selection. If, for example, many cases of very slight dementia are included, the figures presented here may be found to have little relevance. For this reason some of the more important factors determining the nature of this material are worth discussing.

The cases of organic dementia coming to the National Hospital are by no means representative of the condition. For example, cases showing the typical picture in which further investigation is not thought justifiable will be less often referred; or again, cases with excitement as a prominent early symptom are likely to be sent to a mental observation ward and thence to a mental hospital and so never to appear in our series. Even after admission to the wards, by no means every case of dementia is

investigated with an A.E.G. Different physicians vary in their zeal for special diagnostic techniques and change their habits as experience teaches them. One operable tumour masquerading as Alzheimer's disease but diagnosed too late will lead to a flurry of radiological investigation and biopsies. Our material has been amassed by more than a dozen different physicians over a period of four years, and so the selection of an exactly comparable group is not to be expected.

The recognition of dementia depended more on current clinical practice than on explicit criteria, and inspection of the records often raised doubts as to whether correct deductions were drawn from the patient's behaviour. It is notoriously difficult to assess quickly the intellectual capacity in some cases of Parkinsonism, depression with hypochondriasis or dysphasia, for example, and often no searching attempt was made as its clinical significance might at the time seem to be small.

The assessment of cerebral atrophy in the A.E.G. has been described briefly, but the limits of normality are not certain and minor discrepancies were found between the readings of several radiologists. Observer error is notorious in all medicine and the radiologists have gone some way towards estimating it (Birkelo, Chamberlain, Phelps, Schools, Zacks, and Yerushalmy, 1947). But in this study no measures were made of inter-individual or intra-individual reliabilities, and the results once more reflect routine practice of a high standard rather than a precise research technique.

Lastly, the clinical diagnosis was rarely confirmed by post-mortem studies or even by long-term follow-up. But by restricting the material to patients over the age of 45 and by excluding various recognizable diseases, a fairly common and clear-cut clinical problem was investigated even though a number of different disease processes were included.

Summary

In routine clinical practice at least 85% of 68 cases of unexplained dementia in later life showed evidence of cerebral atrophy in the A.E.G.

In 213 A.E.G.s performed in the investigation of cases without dementia 11% showed an unexplained cerebral atrophy, and these were most commonly associated with epilepsy of late onset.

Features of the A.E.G. that suggest an associated dementia are cortical sulci greater than 0·5 cm., air trapped in the insular region, and enlargement of the lateral ventricles particularly marked in the region of the trigone.

The author was seconded from the Maudsley Hospital, London, while this work was being done, and he wishes to thank Dr. J. St. C. Elkington for suggesting the investigation and for many helpful criticisms, and the Medical Committee of the National Hospital, London, for allowing him to use the clinical records of patients under the care of various physicians. He owes a special debt of gratitude to Dr. Gordon Thomson, who did all the radiological work, and wishes to thank Dr. E. A. Carmichael, Dr. Hugh Davies, and Dr. Vera Norris for reading the manuscript.

References

Birkelo, C. C., Chamberlain, W. E., Phelps, P. S., Schools, P. E., Zacks, D., and Yerushalmy, J. (1947). *J. Amer. med. Ass.*, **133**, 359.

Chodoff, P., Simon, A., and Freeman, W. (1948). *Amer. J. Roentgenol.*, **59**, 311.

Davidoff, L. M., and Dyke, C. G. (1951). *The Normal Encephalogram*, 3rd ed. Kimpton, London.

Davies, H., and Falconer, M. A. (1943). *Journal of Neurology, Neurosurgery and Psychiatry*, **6**, 52.

Evans, W. A., Jr. (1942). *Arch. Neurol. Psychiat., Chicago*, **47**, 931.

Heinrich, A. (1939). *Z. Altersforsch.*, **1**, 345.

Lysholm, E. (1935). *Acta Radiol., Stockh.*, Suppl. XXIV.

McMenemey, W. H. (1941). *Journal of Neurology, Neurosurgery and Psychiatry*, **4**, 48.

Morel, F., and Wildi, E. (1953). *Schweiz. Arch. Neurol. Psychiat.*, **72**, 211.

Rothschild, D., (1941). *Amer. J. Psychiat.*, **98**, 324.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 134.

CHOROID PLEXUS PAPILLOMA CAUSING SPONTANEOUS SUBARACHNOID HAEMORRHAGE

BY

J. ERNSTING

From the Guy's-Maudsley Neurosurgical Unit, London

Intracranial aneurysms, arteriovenous malformations, vascular tumours, and certain of the bleeding diseases are recognized causes of bleeding into the subarachnoid space. The following case represents an unusual cause, which, although it has been recognized at necropsy, does not appear previously to have been diagnosed and treated during life.

Case Report

A machine operator, aged 26 years, referred by Dr. Brian Stanley, was admitted to the Unit complaining of headache and neck stiffness of eight days' duration. In July, 1951, he had had a previous attack of severe headache, vomiting, and photophobia. He had been admitted to another hospital where the cerebrospinal fluid was found to be xanthochromic suggesting that a subarachnoid haemorrhage had occurred. No obvious localizing signs were observed in the central nervous system and bilateral carotid arteriograms were normal. After a month's bed rest he was discharged as recovered. About a year later a second attack of severe headache occurred and lasted for two days. Then on January 12, 1954, while gardening at home a further sudden severe headache developed followed by vomiting and photophobia, and he was admitted to hospital the next day. Here he was found to be mildly confused, to have marked neck stiffness, and a left pupil which did not react to light. Lumbar puncture yielded a grossly blood-stained xanthochromic fluid. On January 20, 1954, he was transferred to this Unit. On examination on admission he was a well developed young man who was still slightly confused. The abnormal neurological signs included a slight nominal dysphasia, a right upper quadrantic homonymous hemianopia, a slight right lower facial weakness, and a slight left-sided deafness of middle-ear type. Examination of the other systems yielded no further abnormality.

Plain radiographs of the skull were normal.

Left carotid arteriography (Dr. R. D. Hoare) showed good filling of the internal carotid artery and of the left anterior and middle cerebral arteries. An intracerebral vascular lesion, consisting of a fine network of vessels, measuring 3 cm. in its antero-posterior diameter and 1·5 cm. in its vertical diameter, was demonstrated in the left posterior temporal region (Fig. 1). It was supplied by a vessel arising from the internal carotid artery just proximal to its bifurcation, presumably the left anterior choroidal artery. The lesion was not subsequently demonstrated by vertebral arteriography, even though the posterior cerebral artery was filled. This supported the view that it was the anterior choroidal artery which was supplying the lesion.

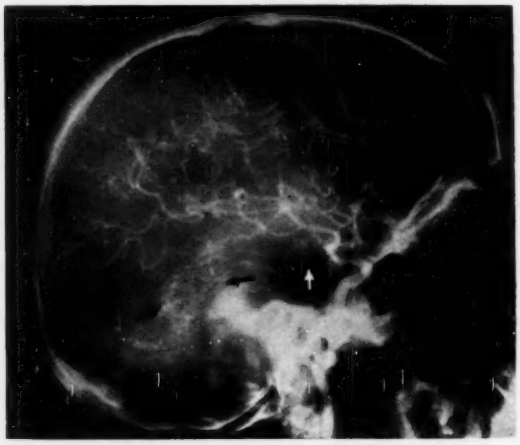


FIG. 1.—Left carotid arteriogram showing a fine network of vessels (indicated by black arrows) supplied by anterior choroidal artery (white arrow).

FIG. 2.—Left lateral ventricle outlined by lumbar encephalography showing a filling defect in the trigone of the left lateral ventricle.

FIG. 3.—Biopsy smear showing cauliflower-like papillomatous tumour (H. and E. × 30).

FIG. 4.—Section of specimen showing in lower half angiomatous tufts, above which, on the left, is an old organized haemorrhage, and, on the right, a recent haemorrhage (H. and E. × 50).

Lumbar encephalography (Dr. R. D. Hoare) showed good filling of the whole ventricular system. The septum lucidum was displaced slightly to the right of the midline, and there was slight dilatation of the left occipital and temporal horns. A spherical filling defect occupied the greater part of the trigonal region of the left lateral ventricle and appeared to change its position with alterations in the posture of the head (Fig. 2). A comparison with the arteriograms showed that this filling defect lay in relation to the vascular lesion. These findings were interpreted as a vascular tumour in the left posterior temporal region which had given rise to a clot within the left lateral ventricle.

Operations.—Two operative explorations of the left temporo-parietal region were carried out. On February 11, 1954, a left lateral osteoplastic flap was turned exposing the convexity of the temporal lobe and neighbouring regions, the surface of which appeared normal. On needling the temporal lobe a firm texture was felt at a depth of between 2 and 3 cm. throughout most of its inferior part. Aspiration at a depth of 2 cm. in the middle temporal gyrus a little anterior to the vein of Labbé yielded fragments of tissue which were subsequently shown on histological examination to be abnormal choroid plexus (Fig. 3). They consisted of vascular tufts covered with cuboidal and columnar cells ; in some parts the tufts were matted together with collagenous material presumably resulting from previous haemorrhage. Aspiration at a point further posteriorly yielded 5 ml. of brown fluid containing blood clot. A horizontal incision was then made in this region, and this opened into the temporal horn where a matting of the choroid plexus was found. The structures in the floor of the temporal horn were discolored and indurated, arousing suspicion of an infiltrating glioma. Consequently a small piece of tissue here was taken for examination before the craniotomy was closed. The histological report was of brain tissue showing reactive changes only (Dr. D. Naidoo).

On February 19, 1954, the flap was therefore re-opened and the incision into the temporal horn was extended. Further scrutiny revealed a localized enlargement of the choroid plexus in the posterior part of the temporal horn. This enlargement measured 2 cm. in width, 0·5 cm. in thickness, and extended for 3 cm. anteroposteriorly. Its surface was indurated and brownish. On either side of it the plexus appeared normal. No seedling tumours were seen in the ventricle. The enlarged portion was then removed, and in the process a small artery was found entering its base. Presumably this was the anterior choroidal artery which had been disclosed in the arteriograms.

The specimen was examined histologically by Dr. D. Naidoo who reported that the appearances were those of a choroid plexus papilloma (Fig. 4). The material showed rather loosely packed tissue containing numerous vascular, almost angiomatous, tufts covered with cuboidal cells. In some areas there were cuboidal and columnar cells heaped up in many layers. There were numerous areas of recent haemorrhage. There was evidence of fibrosis around some vessels, probably as the result of an older haemorrhage.

Progress.—The early post-operative period was uneventful apart from a few focal epileptic attacks and a moderate nominal dysphasia. He was discharged home a month later, when the dysphasia was minimal and the

facial weakness very slight, but the upper quadrantic field defect was increased. Further arteriograms had shown that the vascular lesion had disappeared, and a second encephalogram demonstrated that the filling defect was absent.

When seen at the follow-up clinic three months after the operations he stated that he felt first class, and that he had returned to work as a plastic moulder a fortnight previously. There was only a very slight dysphasia, no facial weakness, and the field defect was unchanged. A letter from the patient eight months after operation said that he was very well, and had not lost a day's work. The letter did not disclose any dysphasic difficulty.

The occurrence in this patient of two, or perhaps three, episodes of subarachnoid haemorrhage and their association with signs of a lesion in the left temporal lobe, suggested at first the possibility of an aneurysm of the left middle cerebral artery. This diagnosis, however, was ruled out by the neuroradiological findings, which in view of their unusual character were deemed to indicate a tumour. It was not until the biopsy findings obtained at the first craniotomy were completed that the true nature of the lesion—a choroid plexus papilloma—became known. That this papilloma had been responsible for the attacks of intracranial haemorrhage was strongly suggested by the macroscopic appearance of matting around the lesion, and confirmed by the histological evidence of past haemorrhage within it.

Discussion

Most cases of subarachnoid haemorrhage are due to leaking intracranial aneurysms, while leaking arteriovenous malformations (cirsoid angiomas) are the cause in from 5 to 10%. In all the published studies of subarachnoid haemorrhage, however, there has been a residuum of cases in which the source of the bleeding could not be found. Thus no lesion was demonstrated in 16% of Taylor and Whitfield's (1936) post-mortem series, in 18% of Richardson and Hyland's (1941) necropsy studies, and in 20% of Falconer's (1951) patients investigated by arteriography. The case reported here represents an additional cause, which may possibly account for some of those cases in which hitherto no cause for the bleeding has been found.

Spontaneous subarachnoid haemorrhage is an uncommon presenting feature of a choroid plexus papilloma but it has been found at necropsy (Graves and Fliess, 1934; Friedman and Solomon, 1936). In these cases the tumour was found to be haemorrhagic and the cerebrospinal fluid was either frankly bloodstained, or xanthochromic. No report of a case diagnosed during life appears to be present in the literature.

In the usual routine necropsy of a case of subarachnoid haemorrhage the brain is removed in one piece, the circle of Willis is examined for the presence of an aneurysm, and the brain is then cut into slices. Even with an adequate inspection upon these lines a small papilloma of the choroid plexus might remain undiscovered and the cause of the haemorrhage pass unrecognized, the presence of bloodstained fluid in the ventricle being regarded as a contamination carried in by the knife. (Such a mistaken interpretation would be avoided if the brain were always first fixed in formalin before section.) Clinically the detection of a papilloma causing subarachnoid haemorrhage will rest principally upon arteriography, but it is possible that a small papilloma may bleed into the ventricle and yet not be apparent in the arteriograms. Thus these lesions may well be commoner than has been hitherto supposed.

I wish to thank Mr. Murray A. Falconer, who operated on the patient, for his permission to publish this report, Dr. R. D. Hoare for the radiological studies, and Dr. D. Naidoo for the pathological reports.

References

Falconer, M. A. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 153.
Friedman, J. J., and Solomon, C. I. (1936). *Amer. J. Dis. Child.*, **52**, 114.
Graves, G. W., and Fliess, M. M. (1934). *Ibid.*, **47**, 97.
Richardson, J. C., and Hyland, H. H. (1941). *Medicine, Baltimore*, **20**, 1.
Taylor, A. B., and Whitfield, A. G. W. (1936). *Quart. J. Med.*, **29** (n.s. 5), 461.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 137.

USE OF DEHYDROISOANDROSTERONE IN PSYCHIATRIC PRACTICE*

BY

E. B. STRAUSS and W. A. H. STEVENSON

From the Department of Psychological Medicine, St. Bartholomew's Hospital, London

Having made a preliminary survey of the effect of dehydroisoandrosterone in selected cases of schizophrenia and schizoid psychopathy we decided to investigate a selected group of 11 patients who, irrespective of age, exhibited constitutional immaturity (especially at the emotional level) and who appeared to be inadequate but not psychotic. The patients had previously received psychiatric treatment of one sort or another, but all psychotherapy was avoided so far as possible during treatment, except in Cases 8 and 9 : interviews were restricted to the recording of subjective and objective findings.

Preliminary investigations always included a routine physical examination and urine test, and, where possible, the total 24-hour 17-ketosteroid output, together with an evaluation of the alpha and beta factors, was estimated. (In quite a number of cases the total was low, or the beta factor diminished.) Estimations of the white cell count, differential count, weight, and blood pressure were done in some cases before treatment, and repeated at intervals during treatment, together with a repetition of the total 17-ketosteroid estimation. Wherever possible a Rorschach test was carried out before treatment and repeated after a significant period of medication.

Organon Laboratories supplied tablets, each containing 10 mg. of epi-dehydroandrosterone, the alternative chemical designation of dehydroisoandrosterone, under the trade name of " diandrone".

The cases have been grouped in accordance with their type of response to treatment.

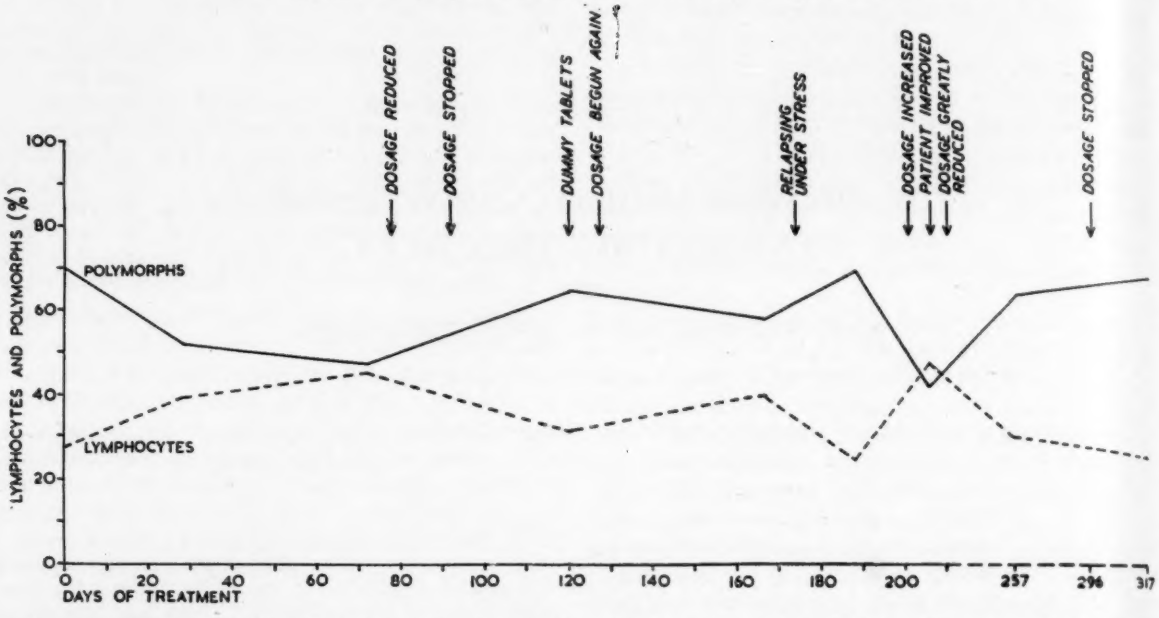
Case Reports

Case 1.—A man, aged 36, was referred by Dr. Gould. The diagnosis was reactive depression in an immature individual of schizothymic temperament. Symptoms included lack of energy, depression, a sense of failure, poorly developed libido, impaired concentration, indecision, feelings of inferiority, shyness, lack of confidence, and apathy. He felt that he was in a mental fog and that life was hard. At his worst moments he was somewhat, but not greatly, relieved by " benzedrine ".

He was treated with " diandrone ", beginning with 5 mg. daily : by the fourth day he felt more alert, more active, more " devil-may-care ", and less depressed. The dosage was increased to 5 mg. twice daily on the 18th day, by which time he was no longer requiring to force himself to perform routine duties and his friends had begun to remark on his improved attitude. Dosage was increased to 5 mg. t.i.d. on the 36th day and gradually reduced from the 78th day, by which time libido was increased, he was enjoying dancing, and had found an improvement in his social contacts and interests. His phases of depression, though present, were not disturbing him, and he was finding his work interesting instead of boring as heretofore. Approximately 14 days after reducing dosage he had two bad bouts of depression and was complaining of lack of energy. Two or three days after treatment was stopped altogether he exhibited a " rebound " phenomenon, in which he improved dramatically and felt as well as he had under treatment. This phase lasted about a week. He was then placed on a week's trial of dummy tablets, which he was told were stronger, and reported his surprise and dismay at noticing no improvement. He was given the correct tablets, again 5 mg. t.i.d., and improved at once, but reported that this time the improvement was general, rather than specific. A month later he said that he felt well, but that he was needing a lot of sleep. It was obvious that he was somewhat depressed and lacked energy. On the 184th day he reported that he had relapsed, with loss of confidence and depression, and said that he had been under increased domestic stress for the previous two or three weeks. Dosage was increased to 25 mg. daily and vitamins exhibited. He improved for four days, then relapsed, but not to his previous low level. Methedrine was given in addition to " diandrone " and vitamins, and the dosage of " diandrone " reduced to 2·5 mg. b.d. The patient then became reasonably stable, and remained well on small doses of " diandrone " and " methedrine ".

*An interim report.

FIG. 1.—The ratio of neutrophil polymorphonuclear leucocytes to lymphocytes in Case 1.



There seemed to be indications that under increased stress dehydroisoandrosterone had lost its effect, as shown by the clinical picture and the alteration in the differential white cell count (Fig. 1). Unfortunately it was not possible to estimate the ketosteroids at this point, and though experimentally perhaps one should have gone on increasing the dose of " diandrone ", the condition of the patient, though willing to collaborate, was such that it was better to give amphetamine. The treatment with " diandrone " was continued nevertheless. The patient made a completely satisfactory recovery, which looks like being permanent, as it has been maintained for some considerable time since " diandrone " was discontinued.

Before treatment the patient's total 17-ketosteroid output in 24 hours was 15·6 mg., of which the alpha fraction was 83·1% and the beta fraction 16·9%. After 48 days' treatment the total output was 19·5 mg., of which the alpha fraction was 67·7% and the beta fraction 32·3%.

Case 2.—A boy aged 14 was diagnosed as an inadequate schizoid personality. Symptoms included a severe stammer since early childhood, tics and mannerisms for three or four years, timidity, lack of confidence, shyness, inability to " mix " or play games. In appearance he was undersized and under-weight, and his voice had not yet begun to break.

He received a 65-day course of " diandrone ", beginning with a daily dose of 2·5 mg. He reported five days later that he could cycle faster. The dose was increased to 5 mg. daily, and two days later he found that he stammered less, that he had more energy and was less timid, and that his appetite had increased. The dose was then increased to 10 mg. daily. He was reported to be talking more freely and had suddenly discovered that he was good at cricket. His mannerisms and tics were vanishing. Two days later the dose was increased to 15 mg. daily. By the 29th day of treatment he had become good all round at games, was anxious not to miss his A.T.C. meetings, had gained in height, no longer allowed himself to be bullied and was becoming more self-assertive and rebellious. By the 44th day of treatment he was reported to be over-aggressive, had joined a mischievous gang at school, was talkative in class and resentful of any discipline. He appeared to be mildly hypomanic on examination, and investigations revealed that he was in fact taking extra doses of the tablets without the knowledge of his parents ; in fact he had been overdosing himself for some time. The daily dose was reduced to 5 mg. He became calmer after 10 days and, though he was still difficult to control, the fault lay mainly in mishandling by his parents, who said that, if anything, he now had too much courage ; for example, whereas he had previously been afraid of the shallow end of the swimming bath, he now practised the crawl at the deep end. His stammer had improved considerably. Treatment was stopped altogether ; a rebound phenomenon occurred one week later, and he described himself as even better than when under treatment. After a further week he had settled down at his new level, decided on a career, and become a fit, healthy, ambitious youngster with, however, some residual stammer. He gained considerably in height and half a stone in weight, and developed secondary sexual characteristics. His parents, having expressed their satisfaction with the result obtained, refused to cooperate in further treatment. He was seen again one year later when he had relapsed considerably.

It was not possible to carry out repeated white cell differential counts on this patient, but counts dore before treatment and one before the end of his course

are well within the normal range and showed no relevant alteration.

His total 17-ketosteroid output in 24 hours before treatment was 4 mg. and on the 34th day 3·85 mg.; the alpha and beta fractions were not fully worked out.

Case 3.—A man aged 26 was diagnosed as an inadequate personality. Symptoms were extreme shyness, sexual immaturity, a marked stammer, and nervous blinking which dated from the age of 5. He had always been timid and lacking in self-confidence, initiative, and drive. He had had about two years of psychotherapy, including hypno-analysis, and his stammer had improved considerably, and he had been able to make friends with a girl. His basic traits had, however, remained unchanged, and a year later he relapsed badly. At this time he had been promoted at work and had become engaged. It was almost impossible for him to use the telephone.

He received systematic treatment, beginning with 5 mg. daily. He noticed the effect about an hour or so after the first dose and by the sixth day felt active and confident, and had been able to lose his temper and deal firmly with a junior in the office for the first time in his life. By the 10th day his fiancée had noticed that he was stammering less, had more energy, more confidence, and was speaking better on the telephone. By the 24th day he had periods when he hardly stammered, and did not mind using the phone. He was realizing how many minor irritations he had had to endure in his domestic setting. It is relevant to note that about the 31st day he began to deteriorate and become depressed. Four days later the dose was increased to 5 mg. three times a day. There was a rapid improvement, so that seven days later he reported that he was able to argue on the telephone, even with a senior. On the 67th day the dose was reduced to 10 mg. daily for three days and then 5 mg. daily for three days. He had deteriorated by the 74th day, but was still, he said, better than before treatment began. The dose was then reduced to 5 mg. 48-hourly and seven days later he reported that he was again unable to use the telephone. Treatment was stopped on the 84th day, and four days later a rebound phenomenon occurred; he felt well, was rather restless, and did not bother to be so obsessionally accurate at work. Fourteen days later, however, he reported that he had relapsed completely, was unable to relax or telephone, and was again stammering badly. He was then placed on dummy tablets and told that they were stronger. He reported after a week's trial that the tablets seemed to have no effect, and he was very worried about it. He was then placed on "diandrone" tablets again and improved at once. His optimum dose was found to be 5 mg. twice a day. He has continued to do well at work, has bought a house, married successfully, and did not stammer during the wedding celebrations, has settled down well, and now has a daughter.

Repeated total and differential white cell counts seemed to show no material alteration in the total count, but there was a slight shift in the relative proportions of the percentage of neutrophil polymorphs to lymphocytes while actually under treatment. This returned to normal when treatment was completed. Before treatment the total white count was 9,000 (polymorphs 61%, lymphocytes 30%, monocytes 7%, eosinophils 2%); on the 165th day of treatment it was 8,000 (polymorphs 50%, lymphocytes, 41% monocytes 8%, eosinophils 1%); and, after treatment, 8,600 (polymorphs 67%, lymphocytes 28%, monocytes 5%).

The total 17-ketosteroid output in 24 hours before treatment was 13·6 mg., of which the alpha fraction was 96% and the beta fraction 4%, and, after 49 days' treatment, 23·5 mg., of which the alpha fraction was 92·5% and the beta fraction 7·5%.

Case 4.—A man aged 20 was diagnosed as a case of reactive depression. Symptoms included pressure-feelings in the head, impaired concentration, inability to carry out his usual tasks without a great effort, and complete loss of confidence.

The patient was placed on "diandrone" empirically and has received 81 days' treatment with 5 mg. twice a day. He has, in addition, received thyroid gr. ½ daily. He has noticed steady improvement in his outlook and states that he has more confidence than he ever had. He is now in the Army and is being considered for commissioned rank. He has also succeeded in developing a well mannered resistance to family pressure.

No 17-ketosteroid estimation or blood counts were carried out on this patient.

Case 5.—This was a boy, aged 18, with factors indicating generalized infantilism with hypogonadal features. The diagnosis was schizoid psychopathy. His illness was estimated as lifelong, but the presenting symptoms had originated at the age of 6. There was an unstable family history and a broken home. Symptoms included fire-raising, and a tendency to run away from home and strip himself naked in the woods. Both symptoms had great sexual significance. He had bizarre religious ideas and was completely unable to adapt himself to everyday life. He had previously been in a mental hospital and had attended special schools. Treatment was begun under the care of Dr. Sands of St. Ebba's Hospital, Epsom. He improved somewhat with educational psychotherapy and testosterone 15 mg. daily. He was given "diandrone" 20 mg. daily five months later and became more normal in every respect. Confidence, energy, output, and ambition all improved and, though libido began to increase, he lost his urges to express it abnormally. He left hospital two months later and successfully adapted himself both socially and occupationally to life with a farming family. He received a maintenance dose of "diandrone" (10 mg. daily) without any signs of relapse, despite considerable domestic stress from time to time. There is no doubt that this patient, who, despite other forms of treatment, remained on the border-line of schizophrenia, became, after two months' treatment with "diandrone", socially adjusted and has been able to live a reasonably normal, though limited life in a normal family. His case has been followed up for 18 months and he has not relapsed. He continued to do well when medication was stopped.

White cell counts carried out before treatment showed an average neutrophil polymorph count of 62% and lymphocytes 30%. In the middle of treatment this had altered to neutrophil polymorphs 52·7%, lymphocytes 33·4%, monocytes 3·3%, eosinophils 9·3%, basophils 1·3%, i.e., there was an eosinophilia, but also once again there appeared to be a slight reduction in the percentage of neutrophil polymorphs compared with lymphocytes.

Case 6.—A man aged 30 suffered from a severe obsessional state. There had at one time been some evidence of schizophrenia beneath the surface. The estimated duration of illness was 15 years. He had a relevant family history and an unstable early childhood. He was extremely shy and retarded, both sexually and emotionally. Previous treatment had included approximately a total of four years' psychoanalysis from three different analysts, a full course of insulin coma, electroplexy, electro-narcosis, and re-educative psychotherapy.

The patient was undergoing a course of ether abreaction and was given " diandrone " to encourage his aggressive abreactive patterns, to increase his confidence, and to combat his shyness. The initial daily dose was 5 mg. The patient's confidence and libido improved considerably, and he was able to hold his own in one or two unpleasant domestic situations—a thing he had never been able to do previously. He said that he felt more on equal terms with people. Treatment with " diandrone " was terminated when he began to complain of increasing depression. It was considered possible at the time that this might be due to the " diandrone ", though the patient was satisfied that the tablets helped him considerably, especially by reducing his fear of people and giving him the confidence to cope with the world better. He had in the course of his treatment found it much easier to approach the opposite sex and had much more desire to do so. Allowance has, of course, to be made for the beneficial effect of the abreactive treatment *per se*. It is, perhaps, worth noting that a depressive phase coincided with a further course of " diandrone ". It is difficult to determine whether there is a causal relationship, as there appears to be in the case of some obsessional patients. The actual effect of the " diandrone " was difficult to assess.

White cell counts were not carried out on this patient, but his total 17-ketosteroid output in 24 hours before treatment was 18·6 mg., of which the alpha fraction was 83% and the beta fraction 17 %, and, after approximately 21 days' treatment, the figures were almost unchanged.

Case 7.—This was a man aged 30 with the physical appearance of a boy of 18 and a diagnosis of inadequate psychopathy. Symptoms included extreme shyness, timidity, self-consciousness, lack of ambition, and loneliness. He had made a suicidal attempt while in the army four years before. He had suffered from pulmonary tuberculosis a year before that. His background was without special features.

He was given a course of methyl-testosterone, 10 mg. daily, for two weeks without any effect, and six weeks later began a 92-day course of " diandrone ", beginning with 5 mg. daily. Apart from a slight increase in energy, there was no response, but on the 15th day he was found to have been dissolving the tablets under the tongue. Four days later, having been instructed to swallow the tablets and the dose having been increased to 5 mg. three times a day, he thought that his voice was deeper and he felt less shy. By the 29th day he was able to control his blushing and was sure that he had improved a little ; and, as he was tending to be irritable, the dose was cut to 5 mg. twice daily. Treatment was stopped 14 days later to assess his physical state, and then begun again on the 50th day. He responded very slowly, but became anxious to join a social club and did not feel so nervous. A situation then arose which made it unwise to continue therapy, but the patient, though still limited socially, has continued to improve and has been able to join various clubs and lead a much more active life with a moderate degree of guidance.

Repeated white cell and differential counts were complicated by monocytosis, for which no cause was discovered. The differential count did show a very slight alteration in the neutrophil polymorph/lymphocyte ratio while he was under medication.

The total 17-ketosteroid output in 24 hours before treatment was 12·8 mg., of which the alpha fraction was 87·6% and the beta fraction 12·4%, and after 79 days' treatment the figures were a total output of 11·6 mg., of which the alpha fraction was 84% and the beta fraction 16%.

Case 8.—This was a man aged 46 with a diagnosis of psychosexual impotence in an individual with a bad family history. The patient, despite a good education and start in life, had never really achieved success in any field. He had ambition, but, as he put it, lacked the drive to achieve his goals. In addition, he was much hindered by a recurrent sexual phantasy which inhibited him in other fields as well. He had been virtually unemployed since the war apart from one or two minor jobs. The patient was treated without success by narco-analysis, testosterone, amphetamine, hypnosis, and was responding slowly to analytical psychotherapy.

In view of the immaturity of his outlook in general, and to his own problems in particular, he was given " diandrone " (10 mg. daily). He reported seven days later that he had more interest in things and that his libido was improving. He found he could discuss his phantasies more easily in the therapeutic session. He decided that they were childish and that he must rid himself of them. The dose was increased to 15 mg. daily with increased improvement. He began to take definite steps to get a job at his own intellectual level. On the 34th day of treatment the dose was increased to 20 mg. daily. At this dosage level he became over-critical and aggressive towards people who took advantage of him and to whom he had previously been over-indulgent. He was aggressive to such an extent that he nearly picked a fight in the street, and his dosage had to be reduced again to 15 mg. daily. From the outset of the " diandrone " medication he cooperated

much more dynamically in his analysis. The patient, having been extremely cynical and critical at the outset, is now extremely enthusiastic about the treatment.

A comparison of the white and differential counts carried out before treatment and on the 72nd day showed once again an alteration in the neutrophil/lymphocyte ratio.

The total 17-ketosteroid output in 24 hours before treatment was 13·7 mg., of which the alpha fraction was 99·3% and the beta fraction 0·7%. On the 72nd day the total output had risen to 23 mg., of which the alpha fraction was 96·5% and the beta fraction 3·5%.

Case 9.—This man, aged 39, was diagnosed as an inadequate schizoid psychopath. It was estimated that symptoms had persisted since puberty (age 12 to 14), and included headache, aches in the genitals and stomach, fears, constant tension, a dread of the worries of everyday life. It was felt that these were basically conversion symptoms which excused him from accepting his own inadequacy as a cause of his lack of success. Treatment had been long and varied, including psychoanalysis, hypno-analysis and re-educative psychotherapy by different therapists. There was a constitutional factor and a neurotic background. "Diandrone" was begun with 5 mg. daily; four days later he said he felt slowed down, outward tension had slackened, he felt different and on the whole better, but could not explain how. The dose was cut to 2·5 mg. daily. Twenty-eight days after treatment began he collapsed into a terror state, stated that he could feel the urge and challenge of life, that it was an upheaval, that he feared the tablets because he realized that he was not yet ready for this access of energy; it was like putting high-octane fuel into a rickety engine. He responded to reassurance, and mild sedation and stopping "diandrone" treatment, but it is of note that the insight he gained caused great improvement in his therapeutic cooperation, to such an extent that about eight months later he became stabilized sufficiently to admit to a 60% improvement in all his symptoms. He now only attends occasionally for follow-up.

White cell counts in this patient showed no significant alteration.

The total 17-ketosteroid output in 24 hours was also within normal limits.

Case 10.—A man aged 24 exhibited acute phobic anxiety and grave motor hysteria. Symptoms included shaking attacks, dyspnoea, an inability to eat in public, to swallow solids, to walk out in the street, or participate in any activity. It was considered that the condition was basically a reaction to a very equivocal home background and certain traumatic experiences. He had had two attacks: the first had cleared quickly following admission to a neurosis centre, the second was of three years' duration and had defied continuous narcosis and other treatments at two different psychiatric hospitals. In view of his lifelong timidity and inadequacy and the total 17-ketosteroid output of 12·7 mg., with a beta fraction of only 0·3 mg., it was decided to try the effect of "diandrone". He was given a daily dose of 5 mg. and responded immediately, being able to walk out in the street and even drive a car for the first time since the illness began. He relapsed, however, by the next evening, but admitted that the tablets had made him feel less frightened and more confident despite himself, and that he now realized that there was a part of him that did not want him to recover. Though "diandrone" treatment was stopped, he cooperated much more fully in his psychotherapeutic sessions thereafter, and improved considerably as a result. We are now of the opinion that "diandrone" should not be used in this type of case, except under strict control and exceptional conditions, because the severity of the anxiety outweighs any advantages to be obtained by forcing the patient to gain an emotionally toned insight too rapidly.

It was impossible to carry out repeated white cell counts on this patient, but those done before and after treatment showed no abnormality.

Case 11.—A man aged 27 was diagnosed as an inadequate psychopath, and it was estimated that he had had symptoms all his life. They included apathy, diminished libido, dyspnoea, migraine, and fatiguability. Before treatment the total 17-ketosteroid estimation was 12 mg., of which the alpha fraction was 83% and the beta fraction 17%. Treatment was begun with 2·5 mg. "diandrone" per day, and one week later he had noticed no difference, except that a "benzedrine" tablet that he took had a "wonderful" effect. The dose was increased to 15 mg. daily, and the patient, on his own initiative, took up to 30 mg. After 22 days' treatment he began to notice some increase in energy and drive, and responded to the challenge with acute migraine. We came to the conclusion that his personality-structure was too poorly integrated for him to be able to benefit from this new source of self-assertiveness and that he was too unreliable and incalculable to justify further treatment with "diandrone" under out-patient conditions. He had a total of 28 days' treatment. It was discovered later that this patient had, in fact, concealed much of his history and past behaviour.

The white cell count carried out on the 26th day of treatment was as follows: total 3,500 (neutrophil polymorphs 47%, lymphocytes 48%, monocytes 4%, eosinophils 1%). A repeat count seven days after stopping treatment was total 5,100 (neutrophil polymorphs 64%, lymphocytes 30%, monocytes 2%, eosinophils 3%, basophils 1%).

Results of Treatment

All the 11 cases described above showed some response to "diandrone". The response to very small doses was rapid in Cases 1 to 6: subjectively, the patients noticed increased confidence, an urge to activity, improvement in libido, increasing interest and awareness of the environment, and an ability to deal with situations which had defeated them in the past. They became less troubled by anxiety in social situations. Objectively, the patients seemed to be less apathetic and more euphoric;

their attitude became more virile and previously feeble heterosexual interests became greatly strengthened. They appeared to become full of energy and drive. There appeared to be an actual increase in the rate of physical maturation in Case 2.

The response was much slower in Cases 7 and 8—weeks instead of days—but the objective picture was the same as in the previous cases, although to a lesser extent. It is noteworthy that Case 8 was able to break free from his infantile sexual phantasies, and that Case 7 showed slight evidence of increased physical maturation.

Cases 9, 10, and 11 exhibited a tendency to gross anxiety, hysteria with marked somatic conversion symptoms, and the effect of " diandrone " appeared to be a challenge to which they responded with increased anxiety. However, the treatment did act as a " catalyst ", in that psychotherapy started after the treatment was more effective in Cases 9 and 10 than it had been previously.

Neither the weight nor blood pressure was materially altered in any of the above cases. A rebound phenomenon has been noticed in some cases when dosage was being cut down: the patient deteriorated, but two or three days after the final cessation he improved suddenly and dramatically, and remained well for up to a week, when deterioration began again. In some cases, however, including one or two other cases not reported here, the improvement continued, as though the patient had found a new normal level. The rebound phenomenon was associated with increased appetite in the euphoric shape, but a blood sugar curve carried out on one case showed no abnormality. In Case 1 it has been possible to continue after the rebound phenomenon with a much smaller maintenance dose. It is interesting to compare this with the steady deterioration which took place when the dosage was being gradually diminished before actual withdrawal. Furthermore, we noted that the mental state tended to vary with the actual dosage in some individuals. Comparing this with the very large doses which have been used by ourselves and others in different cases, it might be that after a certain point, which varies with each individual, is reached an increase in dosage does not produce any further change.

Changes in the Blood

There was an alteration in the ratio of lymphocytes to neutrophil polymorphonuclear leucocytes (the L/N ratio) in the differential white cell count of some patients. The readings in Case 1 (Fig. 1) in response to stress are especially relevant: it might be that dehydroisoandrosterone has a suppressing effect on some stage of adreno-cortical activity in response to stress; in some of the cases where it was possible to make frequent readings, the neutrophil polymorphonuclear leucocytes diminished in relation to the total count when the patient was receiving dehydroisoandrosterone, and returned to pre-treatment level when dosage was stopped, and this shift appeared to be some indication of response to treatment.

We wish to stress that the above conclusions are only tentative and that more study is needed before any definite statements can be made.

The variation was always well within the normal range, and the type of shift was similar. In no case has there been a pathological drop in the total or specific white counts, and in every case these rapidly returned to pre-treatment levels on dropping " diandrone ".

No consistent correlation has yet been found between the alterations in mental state and behaviour and the total 17-ketosteroid output, nor does the ratio between the alpha and beta fractions appear to be very significant, though there may be some importance in the relationship between the amount of alpha-ketosteroid present and the body-weight. We have, however, come to believe that a 17-ketosteroid output which is apparently within normal limits is not to be regarded as a contraindication to treatment with dehydroisoandrosterone, if the clinical or Rorschach indications are favourable.

Conclusions

It is clear that dehydroisoandrosterone altered the behaviour-patterns and mental attitudes in this series of patients, who are probably representative of a small group of persons who exhibit immaturity in one form or another. They are often—probably incorrectly—labelled as inadequate psychopaths, whose response to life is a withdrawal in the direction of schizophrenia, and who have failed to develop satisfactorily either as introverts or as extroverts. All the patients in this series exhibited the schizothymic temperament, in so far as shyness, feebleness of sexual drive, lack of initiative and decisiveness were common characteristics.

Rorschach tests suggest that treatment with " diandrone " enables this group to develop the personality structure which might have been considered to be natural for them.

Dosage should be small in the first instance, 5 mg. daily at the most, and, taking the condition of the patient as a guide, gradually increased over the subsequent weeks. Symptoms of over-dosage include restless activity and euphoria, amounting in one case to mild hypomania, and increased aggres-

siveness, to the point of being quarrelsome and domineering. General experience has shown that there may be a synergistic action with the amphetamines, considerably enhancing the euphoric effect of the latter. Experience showed that if the total daily intake of dehydroisoandrosterone was given in one dose there tended to be a falling off in the effect, with a resulting depression some 10 or 12 hours later. This reaction has been abolished by dividing the daily dose, no matter how small.

The patients who were given dummy tablets noticed the difference, even when led to believe that the inert tablets were, in fact, stronger.

Indications for Treatment

Individuals similar to the group described above, and the psychotics described in our previous paper (Strauss and others, 1952), are at present the only ones of whom we have direct experience. Dr. Sands, of St. Ebba's Hospital, Epsom, has been working with different age-groups.

Any evidence of antisocial behaviour, sexual or otherwise, and any history of undue aggressiveness and explosiveness is a contraindication to treatment with " diandrone ", especially under out-patient conditions.

Fourteen patients were given the Rorschach test by our psychologist, Miss M. Holt, before treatment with dehydroisoandrosterone, and eight afterwards.

The pre-treatment results show evidence of immature personality, poor human and social relationships, schizoid traits, and verbalism.

The patients appeared to conform in showing a constricted and impoverished personality type, such as might come under Rorschach's " coarcted " classification, where both introversive and extroversive tendencies are present to a small extent only. It would appear that the condition termed by Rorschach " ambiequality ", in which the patient remains poised, as it were, and unable to develop fully in either direction (little mentioned by any writer) characterizes patients who subsequently improved with " diandrone ".

Striking corroboration is also provided by the fact that after treatment the patients show a definite personality swing to one or the other side, i.e., show either marked introversive or extroversive characteristics.

Patients whose personality patterns as exhibited by the Rorschach test have differed markedly from the above and have been given " diandrone ", have proved to be unsuitable subjects.

Other points which may prove to be of importance are an increase in the clarity of perceptual appreciation after treatment, which we are now starting to measure, and a change of attitude or orientation towards the same basic concepts still held by the patients, which is of importance in regard to their personality changes.

Discussion and Summary

Whether " diandrone " turns out to be of therapeutic value in psychiatric practice, taking a long-term view, remains to be seen. Certainly, its random use is bound to give very disappointing results ; the case-material has to be selected and controlled with great care and circumspection. However that may be, our research up to date has presented us with quite fascinating problems, for we appear to have at our disposal a chemical agent that can exert a direct and prolonged action on the mental state and may, after protracted use, even initiate subtle changes of a biochemical nature which, in some cases, appear to perpetuate the desired mental improvement after the drug is withdrawn.

The key to the situation is perhaps to be found in the concept of immaturity. Psychiatrists are always using the term in a loose kind of way, sometimes almost as a mild term of abuse, but without very clear ideas as to what constitutes immaturity at the various levels and in the different age-groups.

Recent, as yet unpublished, work in the field of electroencephalography in England has tended to show that electroencephalography can reveal with any certainty as yet only three main types of abnormality : focal lesions, epilepsy, and " immaturity ". In fact, all the abnormal E.E.G. patterns that are not quite clearly focal or epileptic seem to indicate immaturity, and the psychiatric investigation of all patients exhibiting those particular aberrant kinds of wave-forms shows them to be " immature " in the sense in which we have used the term throughout this paper.

It has occurred to us that if one cares to review a whole group of abnormal mental states which have heretofore been correctly diagnosed in accordance with valid current concepts, they could perhaps be regarded *en masse* as varieties of the " immaturity syndrome." Such disorders would include many instances of schizoid psychopathy, schizophrenia-like psychoses of adolescence, retarded puberty, pubertal crises, general " nervousness " manifested as crippling lack of self-confidence, and, possibly, many cases of nocturnal enuresis in older children. If that idea should prove to be well founded and not just wishful thinking, it would suggest that psychogenesis in many of these conditions is of secondary, rather than primary, significance.

Delay in maturation or failure to mature at the various psychosomatic levels coincidentally must

bring in its wake a certain absence of " vitality " (we are sorry to use so vague a term), a lack of self-confidence leading to inefficacy in dealing with the normal strains and stresses of life, all kinds of secondary psychogenic reaction formations and, in the predisposed, withdrawal from the unequal battle in the direction of schizophrenia (whatever that is).

It does, however, seem that we have in " diandrone " a means of treating, anyhow for the time being, some of the grosser features of the immaturity syndrome. At any rate, it provides indications for subsequent research on similar lines by teams of workers—psychiatrists, endocrinologists, and later, perhaps pure biochemists—who have come to understand and sympathize with each other's viewpoint and discipline. A start perhaps has already been made, for a team of clinical and laboratory workers interested in the effect on mental states of changes in the body chemistry is already active. For the moment it has been content to call itself the Psychoendocrine Research Group. It is hoped that observations which will prove of both practical and theoretical value will result from this combined effort.

We acknowledge with gratitude the cooperation and help received from Drs. G. Discombe, J. Gould, H. F. W. Kirkpatrick, A. M. Robinson, L. Rose, D. E. Sands, E. F. Scowen and W. J. Tindall, and Miss M. Holt.

BIBLIOGRAPHY

Reiss, M., Hemphill, R. E., Gordon, J. J., and Cook, E. R. (1949). *Biochem. J.*, **44**, 632.
Sackler, M. D., Sackler, R. R., Sackler, A. M., Co Tui, and Ophuijsen, J. H. W. van (1951). *Acta psychiat. neurol. scand.*, **26**, 415.
Sands, D. E. (1954). *J. ment. Sci.*, **100**, 211.
——, and Chamberlain, G. H. A. (1952). *Brit. med. J.*, **2**, 66.
Strauss, E. B., Sands, D. E., Robinson, A. M., Tindall, W. J. and Stevenson, W. A. H. (1952). *Ibid.*, **2**, 64.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 145.

ISCHAEMIC SENSORY LOSS IN PATIENTS WITH SPINAL AND CEREBRAL LESIONS

BY

R. W. GILLIATT

From The National Hospital, Queen Square, London

In an investigation which has already been reported (Gilliatt and Wilson, 1954), sensation in the fingers was studied during periods of ischaemia of the arm, the ischaemia being produced artificially by inflating pneumatic cuffs to above arterial pressure round the limb. In a group of normal subjects examined after the inflation of a pneumatic tourniquet above the elbow, the mean duration of ischaemia required to produce subjective numbness of the finger-tips was 14 minutes, but when patients with peripheral nerve lesions were tested in this way, it was found that sensation failed with abnormal rapidity in areas of skin supplied by a damaged nerve, so that an area in which sensation was initially only mildly disturbed might, within five or 10 minutes, become sharply demarcated from the rest of the hand.

The abnormally rapid failure of sensation during ischaemia in an area of initial sensory impairment did not appear to be due solely to the local effect of asphyxia on damaged fibres, as it occurred in patients with dorsal root lesions and with nerve lesions proximal to the site of the pneumatic cuff. As an explanation it was suggested that while some of the sensory fibres in an ischaemic nerve would be blocked by the ischaemia, a proportion would continue to conduct impulses under the pneumatic cuff; of these, however, a further proportion would be blocked by any lesion at a higher level, so that the total effect on sensation would be an additive one.

This suggested that a sensory deficit at any level in the nervous system might be exaggerated by the addition of a partial peripheral nerve block, the peripheral block by itself being insufficient to produce sensory loss. The present investigation of patients with spinal and cerebral lesions was undertaken to explore this possibility.

METHODS

These differed in certain details from those described in the previous paper. Whereas previously a rubber cuff 6 in. by 15 in. was used, the present experiments were carried out with a standard sphygmomanometer cuff 5 in. by 9 in. In each test the sphygmomanometer armlet was firmly bandaged round the arm above the elbow and then inflated rapidly to 200 to 220 mm. Hg. With the smaller rubber bag the inflation was more rapid than in the earlier experiments, and it was not considered necessary to raise the limb beforehand, as had been done previously to avoid venous congestion. After the inflation of the pneumatic tourniquet the arm was rested comfortably with the palm uppermost, and the finger-pads were firmly rubbed or stroked at half- or one-minute intervals until the patient noticed a change in the sensation aroused.

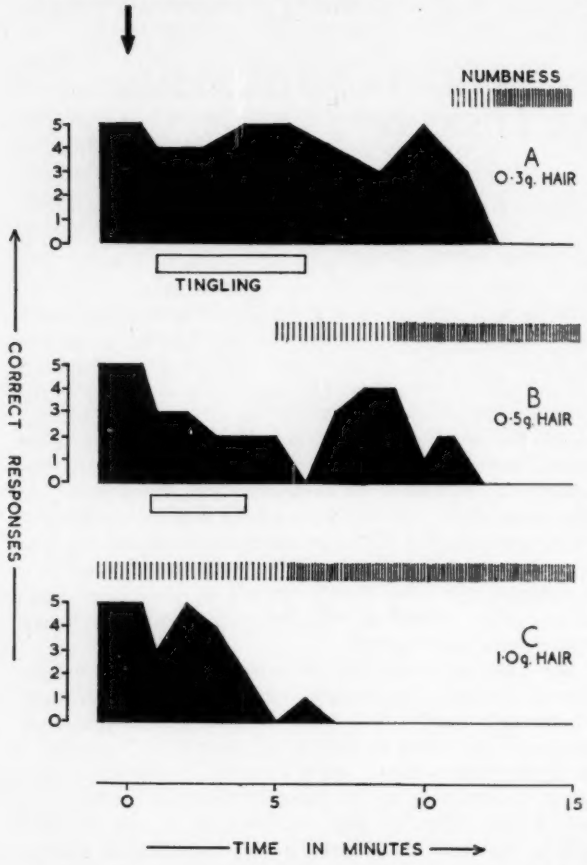
As in the previous work the onset of subjective numbness of the skin of the fingers was easily recognized when it occurred, touches giving rise to an abnormal sensation variously described as "numb", "dead", or "wooden", as if the fingers had "gone to sleep". Patients were rarely in doubt as to the onset of subjective numbness, but when difficulty was experienced it was usually helpful to ask the patient to feel the affected fingers with the other hand. Subjective numbness sometimes included a rough, prickly component, as described by Weddell and Sinclair (1947), but this was variable, and a few patients seemed to develop complete anaesthesia in the finger-tips without noticing in the intervening stages anything suggesting a rough, prickly, tingling, or electric sensation in response to touch.

The earliest time during ischaemia at which subjective numbness was definitely present in the tips of all the digits has been called the "time to numbness". On a few occasions the "time to numbness" was recorded separately for different fingers, but otherwise the term indicates involvement of the tips of all the digits within the time stated.

In three of the patients subjective numbness was already present in the fingers before ischaemia, and these three were therefore asked to say when they considered that the sensation aroused by a firm touch was definitely less than before the test. This was a more difficult subjective change to assess than the actual onset of numbness, but the patients who were examined in this way did in fact give consistent answers in repeated tests.

The methods used to investigate changes in the tactile threshold were similar to those employed previously,

FIG. 1.—Effects of ischaemia of the arm in three patients with disseminated sclerosis. In each case five tests per minute with nylon hair on finger tip. Ischaemia at arrow.



and short lengths of standard nylon suture material, suitably mounted and calibrated, were again used to provide graded tactile stimuli. In some patients an area of skin on the finger-pad was ringed and used for testing, but in those with horny skin the dorsum of the terminal phalanx was preferred. Runs of five stimuli were used each minute, the stimuli being spaced irregularly to prevent guessing. The patient's score was then recorded graphically as the number of stimuli perceived each minute. All tests in the present series were carried out at room temperature.

RESULTS

Patients with Spinal Cord Lesions

Five patients with lesions of the spinal cord in the cervical region were examined. In two patients with cervical cord tumours, the level of the lesion was not in doubt and was confirmed at operation in each case. Three patients suffered from disseminated sclerosis, and in them it is unlikely that the disease was restricted to the cervical region of the spinal cord, although in each case the presence of symmetrical sensory symptoms in the hands in association with spastic paraplegia suggested that this region was severely involved (cf. McAlpine, 1954).

When the circulation to the arm was arrested by a pneumatic tourniquet above the elbow, the " time to numbness " was in every case less than the normal figure of 14 minutes, found previously in 50 control subjects (Gilliatt and Wilson, 1954). In some experiments the " time to numbness " was reduced to less than half the normal figure, and in only two cases did it exceed 10 minutes.

When the effects of ischaemia are compared closely with the results of formal sensory testing it is clear that in general the " time to numbness " was shortest in those with the most severe sensory defects. This is well illustrated by the three patients with disseminated sclerosis (Fig. 1).

Case 1.—Mrs. H. N., aged 52 (N.H. No. 19317), was admitted to the National Hospital under the care of Dr. Denis Brinton on December 13, 1952, with a history of increasing stiffness and weakness of the legs for five years, with occasional loss of sphincter control. Intermittent " pins and needles " in the fingers of both hands were first noticed in 1950, and more recently the fingers had felt numb and had tingled when they were touched.

Examination on admission in December, 1952, revealed pallor of both optic discs but no other abnormality in the cranial nerves. Tone and power in the arms were normal, but the tendon reflexes were abnormally brisk and tactile sensation was impaired in both hands. Severe spastic weakness of both legs was present with extensor plantar responses. Superficial sensation was present in the legs, but vibration sensation was absent below the costal margin, and passive movements of the toes were not perceived.

Sensation in the hands was examined in detail before a tourniquet test on March 1. There had been some improvement since admission, and the fingers no longer felt numb although they still tingled faintly when they were touched. Pain and temperature were perceived normally and light touches with a 0·3 g. nylon hair were felt without difficulty on the finger-tips. There were errors in discrimination of compass points on the finger-pads at 0·5 cm. separation but not at 0·7 cm. Vibration and joint sensation were normal.

The effects of ischaemia of the right arm are shown in Fig. 1A. A sphygmomanometer cuff was inflated to 210 mm. Hg round the arm above the elbow, and within one minute the patient noticed ischaemic tingling in the fingers which persisted for five minutes. During the first 10 minutes of ischaemia the patient missed occasional touches with the 0·3 g. hair but the skin of the fingers did not feel abnormal when it was rubbed until 11 minutes, when the finger-tips were described as " a bit changed and numb ". After 12½ minutes the fingers had " definitely gone to sleep ", and at this time touches with the nylon hair could no longer be perceived.

Comment.—Although in the past this patient had suffered from tingling and numbness of the fingers,

these symptoms had improved, and at the time of testing the hands were normal save for the presence of faint paraesthesiae in the finger-tips and mildly defective two-point discrimination. When the circulation to the arm was arrested by a pneumatic tourniquet above the elbow, subjective numbness of the fingers did not appear until 11 minutes after the onset of ischaemia. Light touches with a 0·3 g. hair were still appreciated at 10 minutes, but were missed after 12½ minutes.

Case 2.—Mrs. A. B., aged 27 (N.H. No. 26919), was admitted to the National Hospital under the care of Dr. Purdon Martin on March 6, 1953, with a history of fluctuating weakness of the legs for three years and of clumsiness of the hands for six months. Examination on admission revealed pathological pallor of both optic discs with a small central scotoma on the right. In the arms tone and power were normal, but the tendon reflexes were abnormally brisk. A severe spastic paraplegia was present with an ill-defined upper level of sensory loss in the lower dorsal region.

On admission the patient complained of numbness of the fingers of both hands with tingling when they were touched, but by the time that an ischaemic test was carried out on March 17 sensation had improved and subjectively the skin felt normal. Pain and temperature were perceived normally, but light touches with a 0·3 g. nylon hair were often missed and there were many errors in two-point discrimination at 0·5 cm. on the fingers. Vibration and joint sensation in the fingers were normal.

A sphygmomanometer cuff was inflated to 210 mm. Hg round the right arm above the elbow (Fig. 1B), and resulted in faint ischaemic paraesthesiae which lasted for three minutes. After five minutes the finger-tips felt numb when they were touched and by nine minutes "much more dead". A 0·5 g. nylon hair was used to test sensation on the finger-pads as the patient perceived this stimulus without difficulty before ischaemia. During the ischaemic tingling, however, touches with the hair were often missed, and after the paraesthesiae ceased the patient's appreciation of the stimulus improved only slightly before failing altogether after 12 minutes of ischaemia.

Comment.—In this patient the tactile threshold was initially slightly raised in the finger-tips, and ischaemia of the arm resulted in more rapid deterioration in sensation than in Case 1, subjective numbness of the fingers occurring after five minutes with complete anaesthesia to a 0·5 g. hair after 12 minutes.

Case 3.—Miss E. W., aged 41 (N.H. No. 10332), was admitted to the National Hospital under the care of Dr. Carmichael on February 12, 1954, with a history of weakness of the legs since 1941, at which time an episode of impaired vision in the left eye had occurred. Examination at the National Hospital in 1945 had shown pallor of the left optic disc, absent abdominal reflexes, and a spastic paraparesis. The arms remained normal until 1951, but thereafter the patient noticed increasing stiffness and clumsiness with numbness of the skin of the hands.

Examination on admission in February, 1954, revealed a severely disabled patient with bilateral optic atrophy, nystagmus, and spastic weakness of all four limbs. All forms of sensation were impaired in the lower limbs and on the trunk below the level of D2, but appreciation of pain and temperature was preserved in the upper limbs. There was, however, subjective numbness of the skin of both hands with a raised tactile threshold to nylon hairs, and the patient made many errors in two-point discrimination on the fingers. Vibration sensation was present but joint sensation was mildly defective in the fingers.

Immediately before a tourniquet test on the right hand on February 15 the patient was unable to feel either 0·3 g. or 0·5 g. nylon hairs on the finger-tips, but made no errors with a 1 g. hair. There were errors in discrimination of compass points on the fingers at 2 cm. separation, but not at 2·5 cm. When the fingers were firmly rubbed the patient described them as "a bit numb" but "not completely dead".

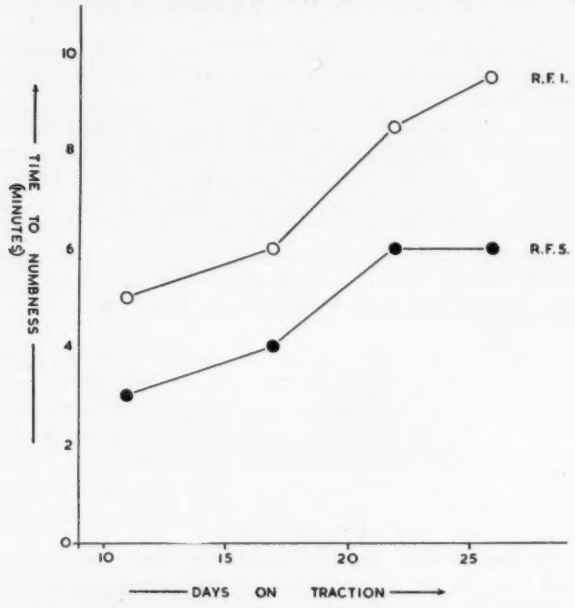
A sphygmomanometer armlet was then inflated to 220 mm. Hg round the right arm above the elbow and resulted in rapid deterioration in sensation (Fig. 1C). Ischaemic paraesthesiae were absent altogether, and after five minutes touches with a 1 g. hair could no longer be felt. At this time the patient first remarked that the sensation aroused by stroking or rubbing the finger-tips was changed, and that they felt more numb and dead than before the ischaemia.

Comment.—This was an advanced case of disseminated sclerosis with moderately severe symmetrical sensory loss in the hands. A pneumatic tourniquet above the elbow resulted in the development of complete anaesthesia to a 1 g. hair after five minutes of ischaemia, with a corresponding increase in the subjective numbness of the skin, a more rapid change in sensation than had occurred in either of the previous cases.

"Time to Numbness" as an Index of Sensory Recovery.—From the results already described, it seemed possible that either improvement or deterioration in a patient's condition might be accompanied by changes in the "time to numbness", which could be recorded by repeated tests with a cuff. To investigate this further, two patients with cervical cord lesions were examined at regular intervals, and changes in the "time to numbness" compared with the results of formal sensory testing.

Case 4.—Fig. 2 shows the results of a series of tests in Case 4, a patient who was being treated by continuous head traction. The patient (N.H. No. 38405) had been admitted under the care of Dr. Denis Brinton with spastic weakness of all four limbs and mild symmetrical sensory loss in the hands. He was thought at first to

FIG. 2 (Case 4).—Cervical cord tumour. Pneumatic tourniquet tests during pre-operative head traction showing " time to numbness " for right thumb (R.F.1) and fifth finger (R.F.5).



be suffering from cervical spondylosis, but at operation (Mr. Harvey Jackson) he was later found to have a small intramedullary endothelioma at the level of C4.

A tourniquet test was first carried out on July 23, 1953, after the patient had been on continuous traction for 11 days. At that time sensation was still impaired in both hands, particularly on the ulnar sides. The skin of the ring and fifth fingers felt " slightly numb " when it was touched, but on the thumb and on the index and middle fingers, touches were described as normal. Pain and temperature sensation were not obviously impaired in the hands, but the patient was unable to feel a 0·5 g. nylon hair on any finger, and made errors in the discrimination of compass points 1 cm. apart on the index. The vibration of a tuning fork was subjectively reduced in the fifth finger compared with the index and thumb. Joint sensation was defective in the fifth finger, but normal in the other digits.

When a sphygmomanometer cuff was inflated to 220 mm. Hg round the right arm above the elbow no ischaemic tingling was felt. After three minutes the patient described sensation in the skin of the fifth finger as " a little worse than before " when it was rubbed, the other fingers being unchanged. After four minutes all digits except the thumb felt " a bit dead " to touch, and at five minutes the thumb was also affected, all digits feeling " dead " and " wooden " when they were rubbed together.

Six days later the tourniquet test was repeated. The patient himself considered that the right hand had improved and that the numbness of the ring and little fingers was less, but examination with nylon hairs and compass points revealed no change. When the pneumatic tourniquet was applied above the elbow, deterioration in sensation in the fifth finger was noticed after four minutes, numbness spreading rapidly across the hand to involve the thumb after six minutes. No ischaemic tingling was felt in this or in subsequent tests.

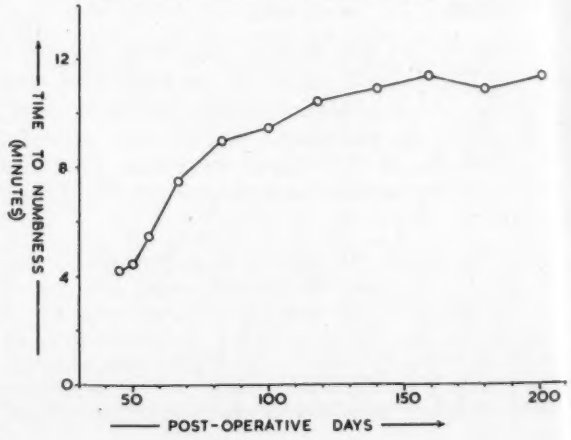
Five days later the patient was re-examined. Subjectively sensation in the right hand was unchanged, and there were still errors in discrimination or compass points at 1 cm. separation on the index finger. A 0·5 g. nylon thread was now occasionally perceived on the radial fingers, but replies were inconstant and the patient tired rapidly. The ischaemic test showed a definite change in that subjective numbness appeared later and spread more slowly across the hand. No change was noticed in the fifth finger until six minutes, and in the thumb the sensation aroused by touch was described as normal until eight and a half minutes.

A final test was carried out on the right hand four days later. The patient himself was not convinced that there had been any further improvement in sensation, and formal sensory testing revealed no change. After six minutes of ischaemia the fifth finger felt " very dead ", but the patient noticed no deterioration in the thumb until 10 minutes. After 11 minutes the thumb was still much less numb than the other digits.

Comment.—In a patient with a cervical cord lesion there was slight but definite improvement in sensation during head traction, which was shown more clearly by the use of ischaemia than by other sensory tests on the hand. Initially there was a difference in sensation between the two sides of the hand, and during traction improvement was more marked on the radial than the ulnar side. Both of these findings were subsequently explained by the discovery of a spinal cord tumour at the level of C4.

Case 5.—A series of ischaemic tests on Case 5 is shown in Fig. 3. The patient (N.H. No. 43140) had been admitted under the care of Dr. Purdon Martin with spastic weakness of all four limbs due to a large neurofibroma at the level of C2. Initially all forms of sensation were severely impaired in the limbs, and superficial sensory loss extended as high as the third

FIG. 3 (Case 5).—Cervical cord tumour. Post-operative tourniquet tests showing recovery of sensation in right hand.



cervical dermatome, but after removal of the tumour by Mr. Harvey Jackson sensation rapidly improved.

The first tourniquet test was carried out on the right hand on April 13, 1954, 45 days after operation. At this time the fingers did not feel abnormal when they were rubbed, and the touch of a 0·3 g. hair was perceived on the finger-tips. Painful and thermal stimuli were also appreciated normally. The patient still made errors in two-point discrimination at 0·7 cm. separation on the finger-pads, but not at 1 cm. Vibration and joint sensation were normal. When a sphygmomanometer cuff was inflated to 210 mm. Hg round the arm above the elbow, no ischaemic tingling was felt. Four minutes after the onset of ischaemia the patient had noticed no change in sensation, but a few seconds later the finger-tips began to feel numb when they were rubbed together, and by five minutes they were described as " dead fingers ".

On the 50th post-operative day a second tourniquet test gave a similar result, but on the 56th day the " time to numbness " had increased to five and a half minutes, and on the 67th day to seven and a half minutes. By this time the patient was usually correct in two-point discrimination at 0·7 cm. separation although he tired easily. When tested with nylon threads, the patient's performance was also greatly influenced by fatigue, and changes during ischaemia were much less constant and reproduceable than the onset of subjective numbness. For this reason the use of nylon threads during ischaemia was abandoned in later tests.

By the 100th post-operative day the patient made only occasional errors in discrimination of compass points at 0·5 cm. separation on the fingers, and the " time to numbness " had increased to 10 minutes. On this occasion the patient first noticed ischaemic paraesthesiae, and described faint tingling beginning two minutes after the onset of ischaemia and lasting for four minutes. Ischaemic tingling recurred in all tests after this time.

Between the 100th and 200th post-operative days there was little change in sensation in the hand. The patient continued to make occasional errors in two-point discrimination when fatigued, and the " time to numbness " did not increase beyond 12 minutes.

Comment.—After the removal of a high cervical cord tumour, the patient was examined at regular intervals for six months. At the end of this time it seemed that improvement in sensation had ceased although recovery was still incomplete and the patient continued to make errors in two-point discrimination when fatigued. During the period of observation there was a progressive increase in the " time to numbness " which appeared to reflect the gradual improvement in function of the cervical cord.

Patients with Cerebral Lesions

Six patients with cerebral lesions were examined. Four of them were suffering from cerebral vascular disease ; the two remaining patients were examined shortly after the successful removal of cerebral tumours.

Shortening of the "Time to Numbness".—In three patients the " time to numbness " was reduced in the affected hand, but in two of them the reduction was small and required simultaneous ischaemia of both arms to demonstrate the abnormality satisfactorily.

Case 6.—Mr. K. I., aged 24 (N.H. No. 50386), a right-handed police officer, was admitted to the National Hospital under the care of Dr. Denis Williams on February 4, 1954, with a history of weakness of the right arm and leg of sudden onset with loss of speech in August, 1952. Some recovery of function had followed, but six months after the onset the patient began to suffer from right-sided and generalized fits.

On admission in February, 1954, the patient showed no evidence of intellectual deterioration, but mild expressive dysphasia was present, with a moderately severe right hemiparesis affecting the arm more than the leg. Sensory loss was restricted to the right side of the face and to the right hand. The patient's blood pressure was 105/60 mm. Hg, and lumbar puncture, air encephalography, and carotid arteriography failed to reveal any abnormality. An electroencephalogram was considered to support the clinical diagnosis of a cerebral vascular lesion.

In spite of minimal dysphasia the patient proved to be an intelligent and reliable witness and detailed sensory examination before ischaemia on February 23 gave the following results. Subjectively the skin of the right hand felt slightly different to the left, but the patient denied that it was actually numb to touch. Light touches with 0·3 and 0·5 g. nylon hairs were frequently missed on the right fingers, but there were no errors with a 1 g. hair. Pinpricks were appreciated everywhere on the right arm and hand, but on the fingers the sensation was subjectively reduced compared with the left. Discrimination of compass points was severely defective on the right fingers and errors were frequent at 2 cm. separation. Passive movements of the right digits were perceived, but the patient's answers were slower and more hesitant than with the left fingers ; the patient was also slow in identifying coins placed in the right hand.

A pneumatic tourniquet was inflated to 220 mm. Hg round the right arm above the elbow and within five minutes the patient began to miss touches with a 1 g. hair on the index finger. After seven and a half minutes he reported that the feeling was " definitely less " when the fingers were rubbed ; by nine minutes the skin felt " very dead " and the 1 g. hair was only occasionally perceived. No ischaemic tingling was felt at any stage.

Comment.—In this patient there was uncertainty as to the pathological nature of the lesion ; the sudden onset of symptoms and subsequent epilepsy had suggested the possibility of spontaneous intracerebral haemorrhage, but no vascular anomaly was demonstrated by arteriography. At the time of examination,

sensory loss in the right hand was mild, but it became appreciably worse within five to seven minutes of the inflation of a pneumatic tourniquet round the arm.

Case 7.—Mr. C. W. (N.H. No. 44726), a right-handed man aged 54, was admitted to the National Hospital under the care of Dr. Purdon Martin on May 4, 1953, with a history of sudden complete paralysis of the right arm and leg with loss of speech in 1948. Recovery of function had been slow and incomplete, and on admission in May, 1953, moderately severe residual dysphasia was present with spastic weakness of the right limbs and considerable sensory disturbance affecting both the arm and leg. The patient's blood pressure was 130/80 mm. Hg and the fundi showed severe retinal arteriosclerosis. Neither lumbar puncture nor carotid arteriography revealed any abnormality, and an electroencephalogram was considered to support the clinical diagnosis of cerebral thrombosis.

Sensory testing was difficult owing to the patient's dysphasia, but examination before ischaemia on May 11 gave the following results. There was subjective numbness of the skin of the right hand and forearm, and pinpricks were reported as dull below the wrist. Fine nylon hairs were not felt on the right fingers and replies were variable with heavier stimuli. Two-point discrimination and joint sensation were severely defective in the right fingers and coins placed in the right hand could not be distinguished. No abnormality was detected in the left hand.

Two sphygmomanometer cuffs were inflated simultaneously round the right and left arms so that the effects of ischaemia could be compared on the two sides. Ischaemic tingling was not significantly different in the two hands, but eight minutes after the onset of ischaemia the patient noticed a change in the right fingers and described them as very dead when they were touched. The left fingers were not subjectively numb to a firm touch until 11 minutes, at which time the patient described the difference between the two hands as much greater than before the experiment. Testing with nylon hairs was not attempted during ischaemia owing to the variability of the patient's replies beforehand.

Comment.—In a patient with moderately severe right-sided sensory loss due to cerebral thrombosis, simultaneous ischaemia of the normal and affected arms increased the subjective difference in sensation between the two sides, a change being apparent to the patient after eight minutes.

Case 8.—Mr. J. G. (N.H. No. 45599), a right-handed man aged 49, was admitted to the National Hospital under the care of Dr. Purdon Martin on June 23, 1953, with the history that five weeks before admission he had suddenly felt giddy and within an hour developed mild right-sided weakness and disturbance of speech without loss of consciousness. At the time of his admission the patient was already greatly improved and speech was normal, but slight spastic weakness of the right arm and leg remained. Sensation was subjectively impaired in the skin of the right hand and foot although tests with compass points and fine nylon hairs revealed no definite sensory loss. The blood pressure was 190/110 mm. Hg and the fundi showed moderately severe retinal arteriosclerosis. Other investigations supported the clinical diagnosis of cerebral thrombosis.

Examination before ischaemia on July 6 showed the sensory disturbance in the right hand to be almost entirely resolved, and the patient himself was no longer aware of any abnormality. There were no differences between the right and left hands for pinpricks, thermal stimuli or light touches, and no sensory inattention to simultaneous stimuli could be demonstrated. Compass points were correctly distinguished at 0·5 cm. separation on the fingers, and joint sensation was normal. Coins were recognized without difficulty when placed in either hand, but the vibration of a tuning fork was felt less strongly on the right fingers than the left.

Two pneumatic cuffs were inflated simultaneously round the right and left arms above the elbows. A pressure of 230 mm. Hg proved adequate for arterial arrest in spite of the patient's hypertension. Ischaemic tingling was much reduced and delayed on the right, but no other sensory disturbance was noted until 12½ minutes when sensation in the right fingers became "a bit dull" to touch. At 14 minutes the patient remarked on "a big difference" between the two hands and described the right as having "wooden fingers". By 15½ minutes, when subjective numbness first appeared in the finger-tips on the left, the whole right hand felt dead and some numbness of the skin had begun to spread above the right wrist.

Comment.—When this patient was examined seven weeks after a cerebral thrombosis, sensation in the affected hand seemed normal save that a tuning fork was felt less strongly than on the other hand. When ischaemia was induced simultaneously in both arms, sensory loss occurred first in the finger-tips on the affected side and spread so rapidly that the whole hand was involved before any change occurred in the normal fingers. Ischaemic paraesthesiae were also reduced on the affected side.

Lengthening of the "Time to Numbness".—From the results described above it seemed possible that the "time to numbness" would be reduced in any patient with pre-existing sensory loss, regardless of the level of the lesion, but in two of the patients with cerebral lesions the expected reduction was not found.

Case 9.—Mr. C. R. (N.H. No. 46951), a right-handed man aged 51, was admitted to the National Hospital under the care of Sir Charles Symonds on August 14, 1953, with a short history of attacks of unconsciousness and of increasing weakness of the right arm and leg. A large left parietal meningioma was successfully removed by Mr. McKissock on August 26, but after operation considerable weakness of the right limbs remained, with moderately severe residual sensory disturbance.

When an ischaemic test was carried out on the 35th post-operative day, no dysphasia remained and the patient was able to cooperate well in the sensory examination. Before ischaemia there was no subjective numbness of the right hand, although light touches were frequently missed and pinpricks did not feel as sharp as on the left. There were many errors in the discrimination of compass points at 0·7 cm. separation on the right fingers. Joint sensation was defective in the fingers and the patient was unable to identify coins placed in the right hand. The inflation of pneumatic cuffs round the arms above the elbows resulted in subjective numbness of the right fingers after 15½ minutes compared with 16½ minutes on the left. Ischaemic tingling was present but reduced on the right compared with the left.

Case 10.—Mr. R. H. (N.H. No. 46118), a left-handed man aged 37, was admitted to the National Hospital under the care of Dr. Purdon Martin on July 20, 1953, six months after a right hemiplegia of sudden onset without loss of consciousness. Recovery had been rapid, and on admission only trivial right-sided weakness remained. The blood Wassermann reaction was strongly positive, but the cerebrospinal fluid was normal.

Before an ischaemic test on July 27 appreciation of fine nylon hairs was normal on the right fingers and no sensory inattention was present. Two-point discrimination and joint sensation were also normal, but the patient had great difficulty in identifying coins placed in the right hand, whereas he made no errors with the left hand. Pain and temperature sensation was normal. Pneumatic cuffs were inflated simultaneously round both arms and resulted in ischaemic paraesthesiae which were equal in intensity on the two sides. After 10 minutes subjective numbness was present in the finger-tips on the left at which time the right fingers still felt normal when they were touched or rubbed. No change was recognized in the right fingers until 12 minutes, but after this time subjective numbness to touch was present and was considered to be equal on the two sides.

Comment.—In the first of these two patients considerable sensory disturbance was present in the affected hand without a significant decrease in the "time to numbness". In the second patient the only sensory function affected was a discriminative one, astereognosis being present without any rise in tactile threshold. In this patient the "time to numbness" was slightly longer in the affected hand than in the normal one.

"Time to Numbness" during Sensory Recovery.—The apparent contradiction between the last two patients and those examined previously was resolved when Case 11 was studied.

Case 11.—The patient (N.H. No. 46232), a right-handed woman aged 45, who was under the care of Sir Charles Symonds, underwent craniotomy for a right parietal meningioma on July 30, 1953; the tumour was successfully removed by Mr. McKissock, but severe left-sided sensory disturbance persisted. Sensation in the left hand was examined at regular intervals for six months, at the end of which time recovery was still incomplete. The results of ischaemic tests during this period are shown in Fig. 4; 10 control observations on the right hand were made, but these were carried out separately from those on the left and no simultaneous bilateral tests were used.

On the 46th post-operative day, when the first tourniquet test was carried out, the patient's speech and mental state were normal, and she was able to cooperate well in the examination. A partial left homonymous hemianopia was present, with a tendency to neglect objects to the left. Moderately severe left-sided weakness was present affecting the face, arm, and leg, but there was no denial of disability or gross neglect of the left limbs. In the left arm and hand there was no loss of appreciation of pinpricks, but left-sided inattention was present on bilateral stimulation. The left fingers felt numb and tingled when they were firmly touched, but the palm and dorsum of the hand were subjectively normal. Fine nylon hairs were not felt on the left fingers, and tactile localization, two-point discrimination, and joint sensation were severely impaired. When a sphygmomanometer cuff was inflated to 210 mm. Hg round the left arm above the elbow, some ischaemic tingling resulted, but this was short-lived, and after four minutes the patient described the sensation produced by rubbing the finger-tips as "much less" than before the test.

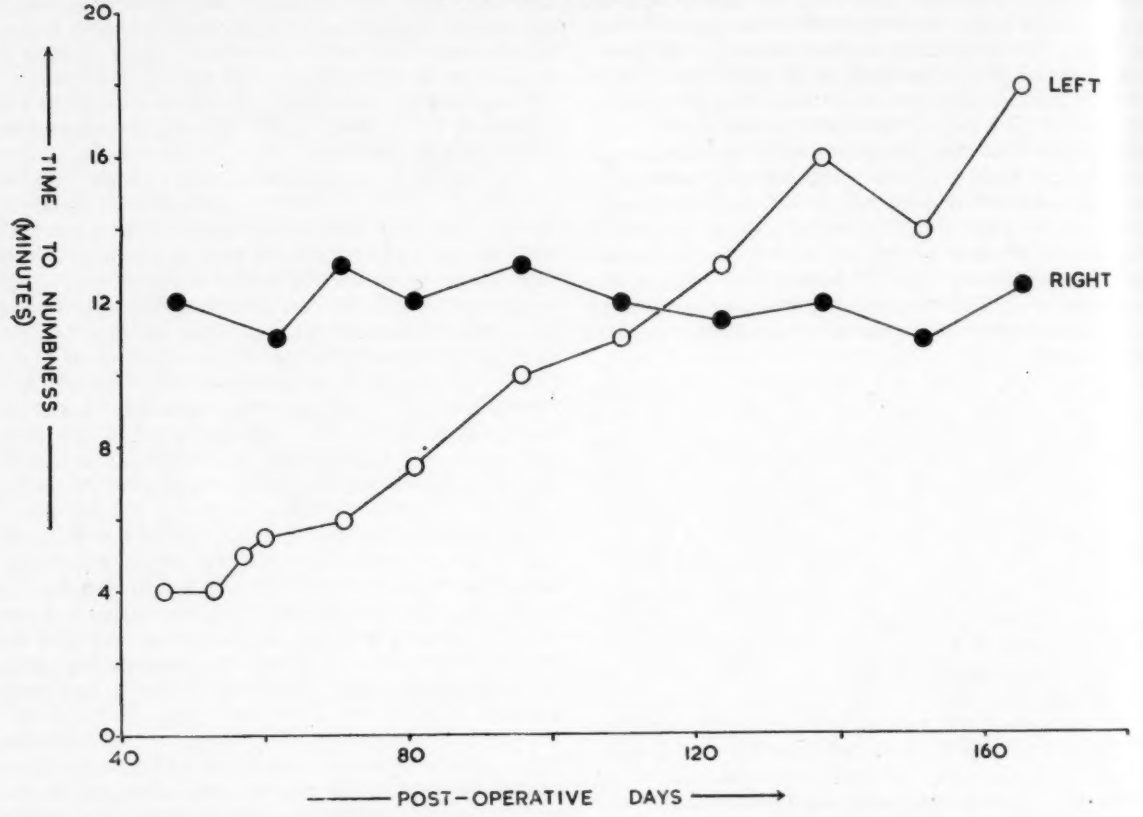
On the 53rd post-operative day there had been some improvement in sensation and the patient was able to localize touches to the correct finger although the skin still felt numb and tingled to touch. When a pneumatic tourniquet was inflated round the arm the finger-tips again felt "dead" to touch after four minutes of ischaemia.

By the 60th day the sensation aroused by rubbing the thumb seemed normal although this procedure still caused tingling in the other digits. However, after five and a half minutes of ischaemia all the digits felt numb to touch at their tips, and no difference could be detected between the thumb and fingers.

By the 81st day the "time to numbness" on the left had increased to seven and a half minutes and by the 110th day to 11 minutes. Although this figure now approximated to the "time to numbness" of the right hand, sensation on the left was still obviously impaired. Subjectively the left fingers felt normal, but a 1 g. nylon hair was only occasionally perceived, and pinpricks felt less sharp than on the right. Sensory inattention to bilateral stimuli was still present and two-point discrimination and joint sensation were grossly defective.

As shown in Fig. 4, subsequent tourniquet tests gave figures for the "time to numbness" in the affected hand which were consistently higher than in the control hand. In the final test on the 166th day ischaemia produced no change in the sensation of touch on the left fingers until 18 minutes, as compared with 13 minutes for the right fingers. In spite of this, sensation in the left hand was still abnormal. There was no subjective numbness

FIG. 4 (Case 11).—Right parietal meningioma. Post-operative tourniquet tests showing recovery of sensation in left hand and control observations on right hand.



of the skin and no sensory inattention, but the 0·3 g. hair was rarely perceived and there were occasional failures with the 0·5 g. hair. The patient still made errors in discrimination of compass points at 0·5 cm. separation but not at 0·7 cm. Joint sensation in the left fingers was defective and the patient was unable to distinguish the texture of different materials when she handled them with her left hand, although she accomplished this without difficulty with her right hand.

Comment.—After the removal of a right parietal tumour sensation in the left hand was slow to recover. At first the "time to numbness" in the left hand was shorter than normal, but as sensation improved the time increased, until after four months it consistently exceeded the normal. At this stage the tactile threshold was only slightly raised, but discriminative sensation was severely affected. Since the patient was unable to distinguish the texture of objects held in the hand, a similar difficulty must have existed when she attempted to assess the sensation aroused by rubbing the finger-pads during ischaemia. It is, therefore, possible that the first changes in sensation produced by ischaemia were ignored on the affected side, resulting in an apparent increase in the " time to numbness".

Discussion

In a previous paper it was shown that in patients with peripheral nerve and dorsal root lesions affecting the hand, the inflation of a pneumatic tourniquet round the arm produced abnormally rapid deterioration of sensation in the distribution of the affected nerve or root. This was considered to be due to the combined effect of the two partial nerve blocks at different levels, one being at the level of the lesion and the other in the peripheral segment of nerve artificially deprived of its blood supply. The present work supports this view, and shows that in patients with spinal or cerebral lesions a peripheral nerve block may also add its effect to that of the central lesion, and result in sensory loss in excess of that caused by either one alone.

In a normal subject, ischaemia of the arm must be maintained for 10 or 15 minutes to cause sensory loss, whereas in a patient with normal peripheral nerves but with a cervical cord lesion, sensory deterioration occurs much earlier during ischaemia. This implies that there is in the normal sensory system a considerable reserve of function, and that a substantial proportion of the afferent fibres from

a given area must fail to conduct impulses before sensory loss can be expected.

From this conclusion several deductions of clinical importance emerge. In the first place it is clear that small nervous lesions are unlikely to give rise to detectable sensory loss ; this must explain many clinical instances of mild peripheral nerve lesions without changes in sensation. Absence of sensory loss in dorsal root lesions is also easily explained since there is, in any case, considerable spatial overlap between adjacent roots. If survival of one half or two-thirds of the normal number of nerve fibres from a given area is sufficient to provide apparently " normal " sensation, it is hardly surprising that complete loss of a single dorsal root does not necessarily result in sensory loss.

In clinical neurology one might also expect to find examples of sensory loss due to the combined effect of two lesions at different levels. It is not uncommon for a patient with disseminated sclerosis to notice that a foot " goes to sleep " with abnormal rapidity when the legs are crossed, a phenomenon which is directly comparable with the effect of a pneumatic cuff, and it is likely that there are other conditions in which the existence of two lesions may result in unusual patterns of sensory loss. For example, the occasional occurrence of sensory loss of a peripheral nerve or dorsal root distribution in a patient with a cerebral tumour may be due to the superimposition of the effects of two lesions at different levels. Certainly a very mild disturbance at a peripheral level would be sufficient to produce its effect in the presence of diffuse sensory loss due to a cerebral lesion. The occasional finding of a sensory level in the dorsal region in a patient with cervical spondylosis might be explained in the same way, a mild and unsuspected dorsal disc protrusion being sufficient to cause this false localizing sign in the presence of some pre-existing sensory disturbance due to a lesion at a higher level.

In the previous paper it was suggested that the use of a pneumatic tourniquet might prove to be of practical value in the investigation of disturbances of sensation. In the diagnosis of peripheral nerve lesions, the test was particularly helpful in patients whose sensory loss was initially too slight and ill-defined to allow accurate demarcation of the area of skin involved. In such cases the effect of ischaemia on adjacent areas of normal skin provided the necessary control against which the behaviour of damaged nerve could be assessed. However, the patients with spinal and cerebral lesions described in the present paper have mostly shown diffuse sensory loss throughout the hand, and in them the effects of ischaemia cannot be interpreted so easily. Since the susceptibility of peripheral nerve to ischaemia varies widely in normal subjects, a single observation of the " time to numbness " may not be helpful unless the patient's normal susceptibility to ischaemia is known.

Although the time of onset of ischaemic sensory loss varies considerably in different individuals, this is not the case when repeated tests are carried out on the same subject. For example, Fig. 4 shows that in Case 11 the " time to numbness " in the patient's unaffected hand was never less than 11 minutes and never more than 13 minutes in 10 consecutive tests over a period of four months. This may be contrasted with the normal range of eight to 18 minutes found in 50 different subjects (Gilliatt and Wilson, 1954). Thus repeated tourniquet tests may be of considerable value in recording slow changes in sensation over long periods of time, and in fact the method has proved sufficiently accurate to reveal gradual changes in the condition of a spinal cord lesion, even when these have been slight and difficult to demonstrate by formal sensory testing. In the case of cerebral lesions, however, a complicating factor has been introduced by the nature of the ischaemic test. The appreciation of a changed sensation in the skin when it is touched or rubbed is a discriminative function of the cerebral cortex, and it is, therefore, defective in patients whose cerebral lesions render them incapable of discriminating texture or shape. When such patients have been tested with ischaemia, the onset of numbness in the fingers has been acknowledged only after a considerable delay and the " time to numbness " has appeared to be longer than normal.

Except in this last group of patients, the onset of subjective numbness has usually proved easier to measure than changes in the tactile threshold. In the present series of tests, as in previous work, paraesthesiae have been found to exert a profound effect on the perception of fine nylon hairs, and tingling which has barely been perceptible to the patient has sometimes caused a sharp rise in tactile threshold. For this reason patients with spontaneous tingling may appear to improve during ischaemia if this causes paraesthesiae to subside ; alternatively patients in whom a cuff produces intense paraesthesiae may fail altogether to appreciate light touches after one or two minutes of ischaemia, but recover later as paraesthesiae decline. On the other hand the onset of subjective numbness of the skin has proved easily recognizable even in the presence of spontaneous tingling, and throughout the present work great reliance has been placed on the patient's description of the sensation aroused by a firm touch or by rubbing the skin.

Sinclair and Hinshaw (1951) reported that ischaemic tingling was diminished or absent in patients with spinal or cerebral lesions causing defective tactile sensibility, and suggested that " It may even be that a diminution in the sensation of tingling affords a more sensitive test for such defects than standard testing methods ". However, the present work suggests that the relation between tingling and tactile loss is not a simple one. In the group of spinal cord lesions, ischaemic tingling was short-lived or absent in all the patients with a raised tactile threshold and a reduced " time to numbness " (Cases 2, 3, and 4), and in Case 5 ischaemic tingling returned as sensation improved after operation. In those with cerebral lesions, however, ischaemic tingling was absent in only one case (Case 6), and reduced or delayed in two (Cases 8 and 9). In Cases 7 and 11 ischaemic tingling was present although there was considerable sensory loss and a reduced " time to numbness " in each case.

Marshall (1952) found that in patients with sciatica due to lumbar disc degeneration, ischaemic tingling sometimes occurred earlier in the affected foot than in the normal one. Marshall explained his results by suggesting that there were degenerative changes in the distal segments of the affected nerve fibres which rendered them more irritable during ischaemia. His results could, however, be explained by the simple additive effect of two separate irritative foci along the course of the nerve, one at the level of the lesion and the other under the pneumatic cuff.

If, in patients with spinal and cerebral lesions, irritable foci at different levels can exert an additive effect, the intensity of ischaemic paraesthesiae would presumably depend upon the response of ischaemic nerve peripherally and upon the amount of irritation and spontaneous discharge occurring in the central lesion. The latter would not necessarily be related to the severity of the lesion in terms of other sensory defects.

SUMMARY

In 11 patients with sensory loss in the hand due to spinal or cerebral lesions, the circulation to the affected arm has been arrested by a pneumatic tourniquet.

When a partial peripheral nerve block has been produced in this way, its effect on sensation has been added to that of the central lesion and has resulted in sensory loss in excess of that produced by either one alone.

In patients with spinal cord lesions, repeated tourniquet tests provide a sensitive method of recording improvement or deterioration in the condition of the patient. In those with cerebral lesions there are, however, objections to this form of test.

I am indebted to members of the staff of the National Hospital for permission to publish details of cases under their care. I also wish to thank Dr. E. A. Carmichael for helpful criticism and advice.

REFERENCES

Gilliatt, R. W., and Wilson, T. G. (1954). *Journal of Neurology, Neurosurgery and Psychiatry*, **17**, 104.
Marshall, J. (1952). *Ibid.*, **15**, 242.
McAlpine, D. (1954). *Arch. Middx. Hosp.*, **4**, 1.
Sinclair, D. C., and Hinshaw, J. R. (1951). *Quart. J. exp. Psychol.*, 3,49.
Weddell, G., and Sinclair, D. C. (1947). *Journal of Neurology, Neurosurgery and Psychiatry*, **10**, 26.

THE FEBRUARY (1955) ISSUE

The February (1955) issue contains the following papers :—

Variations in the Basophilia of Nerve Cells Associated with Increased Cell Activity and Functional Stress. Lárus Einarson and Erik Krogh.

Argyrophile Bodies in the Human Spinal Cord. Marion C. Smith.

Morphological Nervous Changes in Survivors of Severe Jaundice of the Newborn. L. Crome.

Unusually Severe Lesions in the Brain Following Status Epilepticus. A Meyer, E. Beck, and M. Shepherd.

Prefrontal Leucotomy and the Anticipation of Pain. Alick Elithorn, Malcolm F. Piercy, and Margaret A. Crosskey.

Intellectual Changes Following Temporal Lobectomy for Psychomotor Epilepsy. Victor Meyer and Aubrey J. Yates.

Visual Hallucinations of the Self in Organic Disease. Kenneth Dewhurst and John Pearson.

Basilar Impression. D. G. Phillips.

Some Observations on the Electroencephalogram in Cerebral Tumours. J. H. D. Millar.

Alzheimer's Disease with Acne Rosacea in One of Identical Twins. Esther A. Davidson and E. Elizabeth Robertson.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 155.

ANXIETY AND AN AUTONOMIC REACTION TO PAIN

BY

MALCOLM PIERCY, ALICK ELITHORN, R. T. C. PRATT, and MARGARET CROSSKEY

From the Department of Psychological Medicine and the Neurological Research Unit of the Medical Research Council, National Hospital, Queen Square, London, and the Department of Experimental Psychiatry, University of Birmingham

In a previous communication Elithorn, Piercy, and Crosskey (1955) reported changes in autonomic reactivity which followed prefrontal leucotomy. The change in reactivity which was observed was related to the kind of stimulus which elicited the reponse. It was suggested that the autonomic reactions in a painful situation were changed by leucotomy in that there was a marked reduction of the anticipatory component which appears in association with subjective anxiety.

Although the evidence suggested that most of the differences which were observed were directly related to the post-operative changes in the clinical picture, the surgical intervention might have modified autonomic activity in a way which was not closely related to behaviour or to subjective experience. In order further to elucidate the relations which obtain between patterns of autonomic reaction and emotional mechanisms we have undertaken a study of psychiatric patients using a " pain expectancy " technique similar to that used in the studies of leucotomized patients. The autonomic responses occurring with pain and with the anticipation of pain have a more obvious relationship with anxiety than with any other major psychiatric symptom. Accordingly, in this study the guiding principle in interpreting individual differences in autonomic reaction has been the extent to which anxiety was a clinically prominent symptom.

Experimental Methods

The apparatus and procedure employed in this investigation for measuring autonomic reaction was essentially the same as that described in the previous communication and is now described only in outline.

Changes in the electrical resistance of the palmar skin (psychogalvanic responses) were recorded graphically (*a*) following an electrical stimulus to the little finger and (*b*) following a red light which was exhibited for a short interval (about 400 millisec.) eight seconds before the onset of the electrical stimulus. Successive electrical stimuli were increased in intensity in regular steps from a subliminal value to the maximum intensity the subject would tolerate. Preliminary tests were carried out with each subject to determine the approximate intensities at which the stimulus was first perceived and at which it became as much as the subject said he could bear. The voltage increment for successive stimuli was then calculated for the individual subject so that approximately 16 supraliminal stimuli were administered before the subject said " stop ". The procedure was explained to the subject before the experiment began and he was asked to say " stop " when the electrical stimulus became " too painful ". No further electrical stimuli were given after the subject said " stop ", and this was made clear to the subject from the outset. After the subject had said "stop" the red light was exhibited three more times, but it was not followed by a shock. After he had said " stop " the subject was told to expect this. Measurements were also taken of the resting level of skin resistance, skin temperature, and environmental temperature. A graphic record of respiration was also kept and the responses to three maximal inspirations were measured before the start of the main investigation. For this the following procedure was adopted : the subject was told that a white light would flash at 3-second intervals and was asked to count the flashes subvocally and to take a deep breath on every tenth flash. This course was followed to ensure that the response was essentially to the stimulus provided by the respiratory excursion and not merely to the sound of the examiner's voice.

Subjects

Thirty-six psychiatric patients were examined with this technique, and the Table lists the diagnoses and ratings for the prominence of anxiety as a symptom, together with the resting levels of skin resistance and the mean responses to the three stimuli. The diagnoses and ratings for anxiety were made by one of the authors (R.T.C.P.) in the course of a clinical interview. Patients were rated for anxiety on a four-point scale. Ten patients

TABLE

ANXIETY RATING, INITIAL SKIN RESISTANCE, AND MEAN LIGHT, SHOCK, AND DEEP BREATH RESPONSES

Sex	Diagnosis	Anxiety Rating	Initial Skin Resistance in Ohms × 10^3	Mean Light Response in Ohms × 10^3	Mean Shock Response in Ohms × 10^3	Mean Deep Breath Response in Ohms × 10^3
M	Schizophrenia	++++	123	2·1	6·9	2·7
M	Endogenous depression	++++	163	9·8	13·8	13·3
M	Endogenous depression	++++	124	2·6	5·0	5·0
M	Endogenous depression	++++	111	1·6	8·4	4·2
F	Tension headaches	++++	215	1·8	11·9	16·7
M	Tension headaches	++++	151	3·0	8·8	9·5
M	Reactive anxiety and depression	++++	172	3·0	10·7	11·5
M	Reactive anxiety and depression	++++	105	1·0	3·7	1·6
M	Obsessional	+++	197	5·5	17·4	15·0
F	Inadequacy of personality	+++	150	1·0	4·4	2·7
F	Reactive anxiety and depression	+++	101	0·4	1·8	1·2
F	Obsessional	+++	149	1·6	5·1	6·1
M	Reactive anxiety and depression	+++	87	2·7	5·8	1·7
F	Inadequacy of personality	+++	155	0·6	12·0	5·1
M	Reactive anxiety and depression	+++	127	5·1	11·3	11·6
F	Reactive anxiety and depression	+++	103	11·1	16·2	0·8
F	Obsessional	+++	101	2·4	5·6	3·9
M	Obsessional	+++	80	4·2	6·6	3·5
	Mean results for group of more anxious subjects		134	3·3	8·6	6·5
F	Endogenous depression	++	171	4·2	24·4	11·7
M	Tension headaches	++	101	3·2	10·0	12·0
F	Schizophrenia	++	146	0·6	10·1	—
F	Schizophrenia (paraphrenia)	++	97	3·6	8·3	12·8
F	Schizophrenia	++	171	1·7	5·6	14·5
F	Tension headaches	++	178	3·6	13·2	20·8
M	Schizophrenia	++	146	3·7	7·7	6·7
F	Endogenous depression	++	158	0·7	3·2	9·4
M	Inadequacy of personality	+	174	1·2	5·7	11·1
M	Schizophrenia	+	208	1·4	5·9	4·1
M	Endogenous depression	+	221	2·5	19·5	—
F	Migraine	+	150	1·5	7·1	8·1
F	Migraine	+	115	1·9	5·3	8·1
F	Endogenous depression	+	103	5·0	11·0	—
F	Migraine	+	164	0·6	8·3	9·5
F	Migraine	+	168	1·6	12·1	11·3
M	Migraine	+	142	2·0	6·6	10·7
M	Migraine	+	194	8·8	16·8	9·5
	Mean results for group of less anxious subjects		156	2·7	10·0	10·7

One subject was reclassified from an anxiety rating of +++ to ++ before the calculations were made.

were rated + (least anxious), seven as ++, 11 as +++, and eight as ++++ (most anxious). For purposes of analysis we wished to divide the 36 patients into two equal groups: less anxious and more anxious. It was therefore decided to reclassify one of the patients rated +++ to a ++ rating. The author responsible for psychiatric assessment therefore reclassified the patient he considered to be the least anxious of the original +++ group. Patients were not examined as to their autonomic reactivity until after the diagnosis and rating for anxiety had been decided. Each subject was tested with the procedure described above on one occasion only.

Experimental Design and Methods of Analysis

In the study of the anticipation of pain following prefrontal leucotomy we calculated an "expectancy ratio" for each subject. This ratio expressed the quantitative relationship between the autonomic responses to the two stimuli, namely, an electrical stimulus and a red light which regularly preceded the electrical stimulus. This ratio was found to change following leucotomy in that the response to the red light became comparatively smaller. It was considered that this change was compatible with decreased anxiety or decreased anticipation of pain. In that study the expectancy ratio was obtained from the mean responses to the two classes of stimuli and the effect of the intensity of the electrical stimulus on the ratio or on the size of the individual responses was largely ignored. This was possible since the relative change in autonomic reactivity to the two kinds of stimulus following leucotomy was fairly gross and was readily identified in terms of the expectancy ratio.

In the present investigation we have used a modified form of this expectancy ratio and have also employed other numerical criteria which, on theoretical grounds, we believed might reflect individual differences in anxiety or anticipatory tension. As we pointed out previously, it is difficult to interpret psychologically differences between the absolute magnitude of responses in different subjects

or in the same subject on different occasions. The magnitude of a sudomotor response will depend not only upon the experimental variable which is introduced but also upon the state of heat balance, and the latter cannot be controlled without extreme practical difficulties. In investigating these autonomic reactions we have therefore used numerical relationships (usually ratios) between responses to different stimuli, for example, electrical stimulus and warning light, or electrical stimuli of different intensities; or relationships between responses to a stimulus of varying significance, for example, response to a light preceding a weak electrical stimulus and response to the same light preceding an intense electrical stimulus. Since successive electrical stimuli increased in regular steps, the change in the significance of the warning light during the course of the experimental session may be assumed to be directly related to the intensity of the preceding electrical stimulus.

As described above, the patients assessed at the clinical interview and subsequently serving as subjects for this investigation were divided into two equal groups: more anxious and less anxious. It is the differences in the autonomic reaction of these two groups which are reported below. It should be mentioned that the differences in autonomic reaction which we sought to identify in this study were of a much finer degree than those which occurred in patients undergoing prefrontal leucotomy. In the latter the clinical change was usually from a severely disabling neurotic state to a state of greatly reduced anxiety, and in some cases to a state of abnormally low anxiety. In this study we are examining differences between two groups of psychiatric patients, one group being judged clinically to be more anxious than the other. But since both groups consisted of psychiatric patients, both were almost certainly more anxious than a normal population. We are thus distinguishing between degrees of pathological anxiety.

Results

In the Table are shown the skin resistance levels and the mean size of responses for each patient, together with the mean levels and responses for each group of subjects. The magnitude of the response to the electrical stimulus ("shock response") is taken as the greatest fall in skin resistance which occurs following the presentation of the paired light and shock stimuli, the level immediately before the presentation of the light being the base line for the response. The magnitude of the response to light ("light response") is taken as the greatest fall in skin resistance which occurs following the exhibition of the light and preceding the occurrence of the electrical stimulus. It can be seen that the mean resistance level of the more anxious group is lower (corresponding to a higher rate of sweating) than that of the less anxious group. The mean responses to shock and to a deep breath are greater in the less anxious group and the mean response to light is greater in the more anxious group. In addition to the initial resting level, the skin resistance was recorded throughout the session, the general tendency being for the levels to fall as the session proceeded. The mean level of skin resistance of the more anxious group fell 29% from 134×10^3 ohms to 95×10^3 ohms and the mean level of the less anxious group fell 36% from 156×10^3 ohms to 100×10^3 ohms. For the two groups these various measures of autonomic reactivity differ in sign as well as in extent and, with the exception of the responses to the deep breaths, none of the differences attains an acceptable level of statistical significance. Such differences between the two groups in the absolute size of the responses would in any case be difficult to interpret because the part played by the state of heat balance of the subjects is unknown.

Expectancy Ratios

The "expectancy ratio", being largely independent of heat-regulating requirements, provides a more meaningful measure. This is expressed here as the mean reponse to light divided by the mean response to shock. This ratio has been multiplied by 100 to give a percentage rating for "expectancy" and has been calculated for each of the 36 patients. The mean value of this measure of expectancy is higher in the more anxious (31·2) than in the less anxious group (23·4) but the difference does not attain statistical significance. This measure, which was adequate to identify the effect of leucotomy, is evidently too coarse to reveal the differences between our present two groups of psychiatric patients. Accordingly, we sought to employ a ratio which has as its denominator the response to a stimulus of minimal emotional significance. It would seem reasonable to suppose that for both the more anxious and the less anxious patients a maximal inspiration made in accordance with instructions previously given by the examiner would be of minimal emotional significance and that, in both groups, the fall in skin resistance which follows a deep breath would have a considerably smaller "psychological" component than the autonomic responses which follow either the electrical stimulus or the warning light. We have accordingly used the mean response to a deep

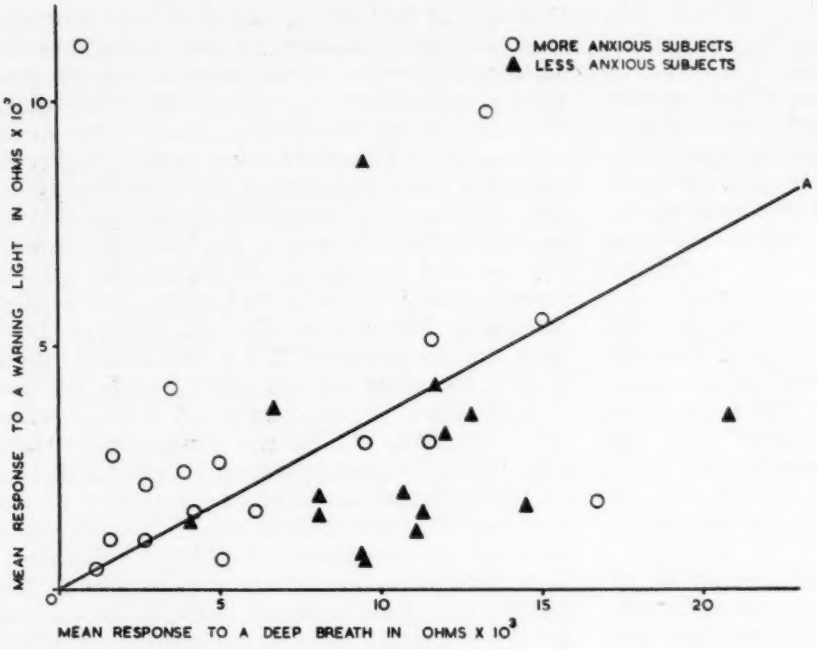


FIG. 1

breath in each subject as a denominator against which to measure the magnitude of the mean responses to warning light and shock. In so far as the response to one kind of stimulus is used as a yardstick against which to measure the response to another kind of stimulus, these two new ratios (response to light/response to deep breath ; response to shock/response to deep breath) are not essentially different from the expectancy ratio, the latter being useful in identifying the effect of leucotomy but not providing a significant difference between the two groups in the present study.

For the more anxious group the mean for the ratio shock response/deep breath response was 1·9 ; for the less anxious group the mean for the same ratio was 0·8. The difference between the two groups is statistically significant at the 0·01 level of confidence ($t = 3{\cdot}33$, $N = 33$).*

The mean for the ratio light response/deep breath response was 0·5 in the more anxious group and 0·2 in the less anxious group. This difference between the two groups is significant at the 0·01 level of confidence ($t = 2{\cdot}579$, $N = 33$). Thus, if the autonomic response to a maximal inspiration is regarded as a measure of " physiological " autonomic reactivity and is used as a base line or denominator, then the responses both to warning light and to shock are relatively greater in the more anxious than in the less anxious group.

The light response/deep breath response ratios are shown graphically in Fig. 1. The ordinate and the abscissa represent the magnitude of response to warning lights and to deep breaths respectively and the position of the circles and triangles shows the relationship between the mean response to the warning light and the mean response to a deep breath in the case of each subject. A line has been drawn to represent the mean ratio for the whole group and it can be seen that there is a tendency for the more anxious subjects to be clustered above the line showing comparatively greater responses to light, and for the less anxious subjects to be clustered below the line showing comparatively greater responses to a deep breath. This diagram shows that in this group of patients there was in 24 (72·7%) of the 33 subjects concordance between the autonomic and clinical criteria of anxiety.

Pain Tolerance

For each subject a record was kept of the lowest perceptible voltage at the finger tips and the voltage at which the subject said "stop" when the intensity of successive electrical stimuli was increased in small steps. The ratio of the highest voltage tolerated to the smallest perceived was designated the " pain tolerance ratio ". The mean value for this tolerance ratio in the more anxious group was 4·82 (range 1·91 to 10·51) and in the less anxious group 4·83 (range 2·45 to 6·89). These two values do not differ significantly. It is therefore most unlikely that any of the autonomic criteria of anxiety reported above which are found to distinguish between the more anxious and the less anxious groups could be accounted for in terms of the intensity of the electrical stimulus tolerated by the two groups.

Effect of Intensity of Electrical Stimulus on Response to Warning Light

The position in serial order of any light stimulus corresponds to the intensity of the electrical stimulus which the light presages, so any habituation which

* The mean ratios derived from a group of individual comparisons are the geometric means and the t tests of significance between such means have been made after a logarithmic transformation of the original ratios. Because three subjects gave unsatisfactory deep inspirations their results have had to be omitted hence $N = 33$ instead of 36.

occurs with repetition of the light stimulus is achieved in the face of the increasing emotional significance of the light stimulus. It is not surprising, therefore, that in both groups of patients the mean response to light at the end of the session is greater than the mean response to light at the beginning of the session. There is, however, a difference between the two groups. The responses of each subject have been divided into quarters corresponding to their serial order in the test session (see Fig. 2) and the measure we have used is the ratio of the mean response to light in the fourth quarter to the mean response to light in the first quarter. This has been calculated for each subject, and the mean value of this measure for the more anxious group is 2·4 and for the less anxious group 1·3. This difference between the two means is significant at the 0·05 level of confidence ($t = 2{\cdot}33$, $N = 36$). Thus the autonomic responses to the warning light of the less anxious group are less affected by increase in the intensity of the electrical stimulus which follows the light than are the corresponding responses of the more anxious group. A similar ratio was calculated for the responses to the electrical stimuli. For the more anxious group the mean of the ratios fourth quarter/first quarter was 3·8 and for the less anxious group 2·8. The two means are not significantly different but the effect is in the same direction as for the responses to the light.

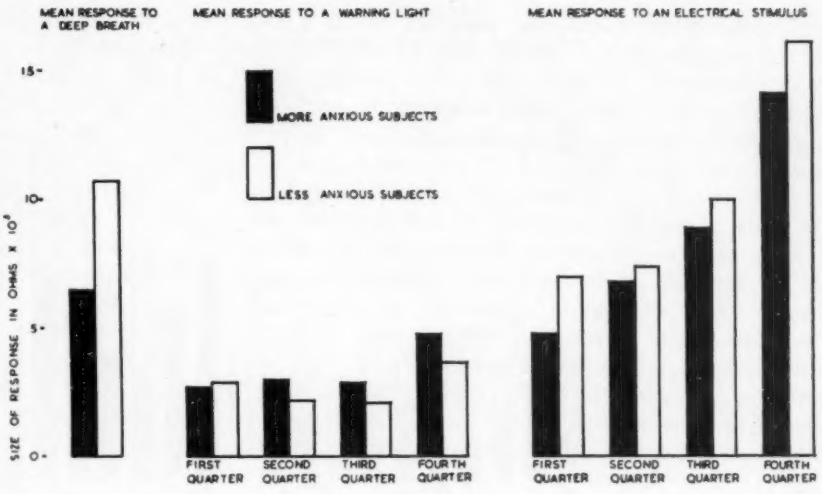


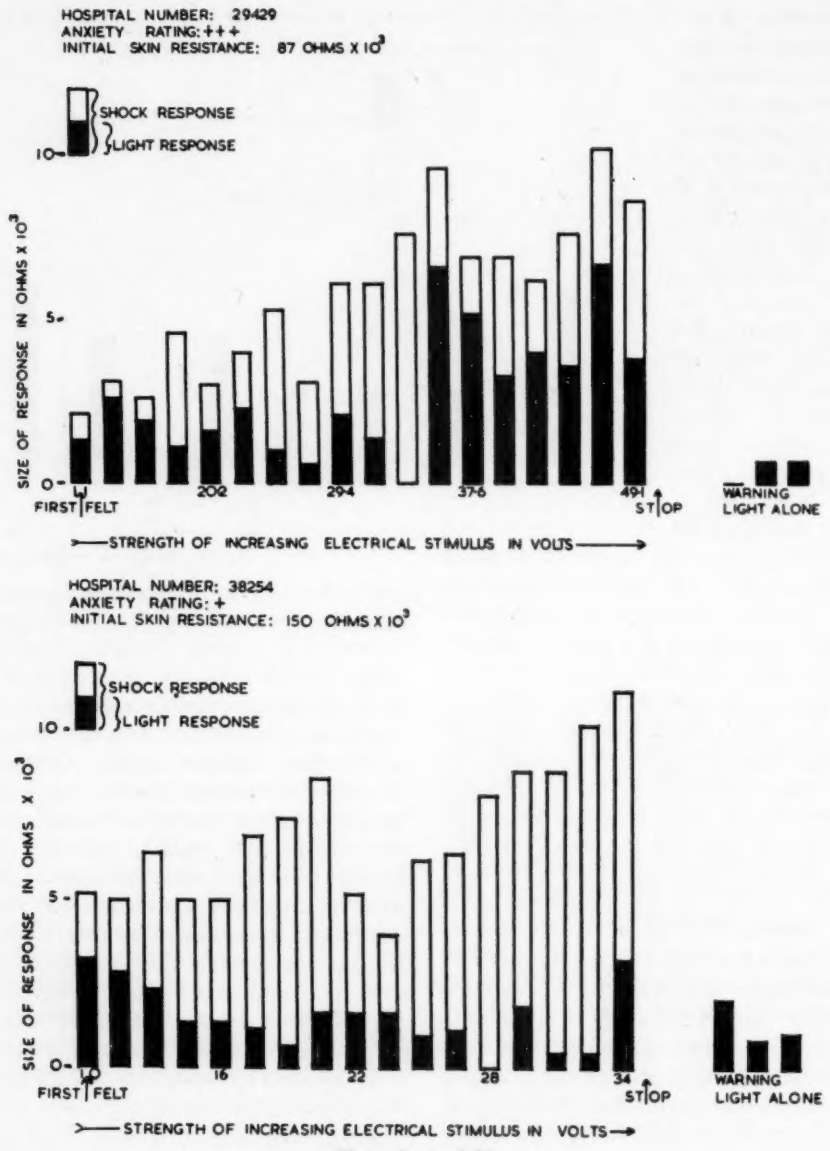
FIG. 2

In Fig. 2 the mean responses of each group to the two stimuli are shown for each of the four quarters. It can be seen that the tendency for responses to light to increase from the first to fourth quarter is more marked in the case of the more anxious group. In the case of responses to the electrical stimulus this difference is less marked and the responses of both groups increase from the first to fourth quarter. Fig. 3 shows the individual responses to light and to shock of two patients ; 3a is typical of the more anxious group and 3b is typical of the less anxious group. In Fig. 3a the responses to light tend to increase with successive stimuli whereas in Fig. 3b some habituation is apparent. Also it can be seen that in Fig. 3a the response to light constitutes a greater proportion of the total response to shock than is the case in Fig. 3b. This effect corresponds to the difference in the " expectancy atios " of the two groups.

Correlation Coefficients

Further evidence concerning the nature of the responses measured in this investigation is provided by the correlations observed between the resting levels of skin resistance and each of the three types of response measured (responses to a deep breath, electrical stimulation, and a warning light). The correlation between skin resistance level and response to a deep breath was 0·585 ($P<0{\cdot}001$), between skin resistance level and response to shock was 0·579 ($P<0{\cdot}001$), whereas the correlation between the skin resistance level and the response to a warning light was only 0·065. (This correlation coefficient is not significantly different from zero but is significantly different from both the other two correlation coefficients when $P < 0{\cdot}05$.) This suggests that the correlation between the resistance level and size of the autonomic response tends to be lower when psychological factors are prominent in determining the response.

If the response to a deep breath is regarded as the best measure of autonomic reactivity to a psychologically neutral stimulus and the response to the warning light as the best measure of autonomic reactivity to a stimulus of emotional significance, the use of the method of partial correlation provides additional information. When the response to light is held constant, the correlation between the resistance level and the response to a deep breath is almost unchanged (0·582) ; when the response to a deep breath is held constant the correlation between the resistance level and the response to light becomes negative though it is still insignificant at 0·016. Response to a deep breath and response to light would appear to be largely



FIGS. 3a and 3b

independent. (The actual correlation between these two variables was 0·133 which is not statistically significant.)

It is perhaps worth noting that if the more anxious group is considered alone then the correlation between the resistance level and the response to light, holding the response to a deep breath constant, is 0·384. This does not quite attain statistical significance but may be regarded as suggestive that the resistance level tends to correlate negatively with a sudomotor response which is determined largely by emotional factors. This would be understandable theoretically and is discussed below.

Discussion

The results of this study suggest that the determinants of the magnitude of the autonomic responses which we have measured are complex.

It has generally been assumed by previous workers in this field that the size of the psychogalvanic response to a particular stimulus bears a direct relationship to the resting level of skin resistance from which the response starts, and indeed it has been the practice of many investigators to express the response as a percentage of the resting skin resistance level (Haggard, 1949; Malmo and Shagass, 1950; Bassett and Ashby, 1954). The

present results show that this relationship can only safely be assumed with stimuli in which the psychological component is small and constant. Thus in the present investigation there are marked correlations between both the resting level and the responses to a shock (0·579) and between the resting level and the responses to a deep breath (0·585) while the correlation between the resting level and the responses to light is negligible (0·065). It would appear therefore that the relationship between the resting skin resistance level (resting sweat rate) and the psychogalvanic response (sudomotor response) depends largely on the nature of the stimulus eliciting the response. In the case of a stimulus which has a minimal emotional significance, such as the deep breath, it seems likely that the size of the response does bear a direct relationship to the resting level of skin resistance. In the case of a stimulus which produces a psychogalvanic response only by virtue of its significance to the subject and not as a result of its own sensory attributes of modality and intensity the situation is more complex. It is reasonable to expect that more anxious people will produce larger responses than less anxious people to emotionally disturbing stimuli, such as the warning light. Now, if heat elimination requirements are kept constant anxious people have lower skin resistance levels than non-anxious people. As a consequence where anxiety is a variable there would be a tendency for the larger responses to be associated with the lower resistance levels. Such a tendency toward a negative correlation might be largely offset by a presumably independent tendency towards a positive correlation. This latter relationship may perhaps be understood most simply if a given stimulus is regarded as a signal tending to cause the organism to reach a certain level of activity rather than as one which causes a certain increase in activity. Thus for a given stimulus low skin resistance levels would be associated with small resistance changes. It is presumably this latter relationship which predominates in the case of the responses to the deep breath and to shock. We suggest therefore that the size and sign of the correlation between psychogalvanic responses and the resting skin resistance depend upon the comparative contribution of emotional or " psychological " mechanisms and more immediate physiological mechanisms.

It is to be expected that emotional factors would be present in the autonomic response to the electrical stimulus. Although this stimulus produces a local reflex response which may even show a local sign (Elithorn and others, 1951) pain is of course necessarily emotionally disturbing. We have evidence also that the electrical stimulus is more disturbing to our more anxious group of patients than to the other group. Thus the ratio of the mean shock response to the mean deep breath response distinguishes clearly between our two groups of patients.

It would seem fair to claim that these observations could be developed to provide a method of estimating the comparative contributions of different levels of autonomic organization in determining the magnitude of a particular autonomic response. In distinguishing between " emotional " and more " local " reflex control of autonomic responses we are, of course invoking a hierarchical organization within the autonomic system and assuming that the " emotional " control of sudomotor responses involves mechanisms which also control many other aspects of behaviour.

There remain to be considered variations within a single test session of the autonomic significance of a physically constant stimulus. We have shown that the ratio of the mean response to light in the fourth quarter to the mean response to light in the first quarter is significantly greater in our more anxious than in our less anxious group. Light stimuli in the fourth quarter differ from light stimuli in the first quarter in two essential ways : position in serial order and the intensity of the electrical stimuli which they precede. By virtue of the factor of position in serial order the higher ratio in the more anxious patients could be accounted for either in terms of poorer habituation or in terms of stronger conditioning. By virtue of the factor of intensity of electrical stimulation the difference between the two groups could be accounted for in terms of accumulating anxiety to an increasingly stressful situation.

We have little evidence to offer as to the importance of conditioning in the Pavlovian sense. We found that responses to the warning light quickly, and often immediately, disappeared when the patient was told there would be no further shocks. This observation is similar to that reported by Mowrer (1938). The responses to a warning light can more fully be described as conditional upon insight and past experience than as simply conditioned by the shock. This does not mean however that conditioning in the Pavlovian sense does not occur. It is possible, for example, that the occurrence of conditioning is merely restricted by other factors such as instructions.

Habituation of the response to light is likely to be important in so far as the light signal is able to initiate an autonomic response before any conditioning has taken place. In ordinary speech we would say that the patient is " anxious " at the

beginning of the investigation before receiving any painful stimuli, and that during the early part of the session this anxiety somewhat decreases (or habituates) and that response to a warning light diminishes correspondingly.

Conditioning and habituation are mechanisms which are familiar to learning theory and are essentially related to the time relations of stimuli and responses. Apart from these mechanisms it is necessary to consider an " anxious " response to a stressful situation. Such a response may be initiated by the instructions of the examiner before the patient has had any experience of the test situation. It may also be aroused by a change in the significance of the stimulus which elicits the autonomic response. Thus it seems probable that the increase in the size of the response to light as the investigation proceeds results at least as much from the shifting significance of this stimulus as from conditioning in the strict sense. This interpretation is supported by the disappearance of the responses to light when the patient is told that there will be no further shocks. Although there is ample evidence for such a mechanism its nature is obscure and would seem to be more appropriately discussed in relation to such concepts as perception and insight rather than in relation to conditioning and learning as ordinarily understood. It may, for example, be regarded as an amplification of classical conditioning mechanisms just as " imprinting " (*Prägung* of Lorenz, 1935) may be considered to be a refinement and limitation of an innate response tendency. Indeed Tinbergen (1951) regards imprinting as a type of conditioning.

At all events it may be said that increased conditioning, reduced habituation, and greater reaction to emotional stress are to be expected in the more anxious patients. These three tendencies would all affect the ratio (fourth quarter light response/first quarter light response) under consideration in the same direction, namely in the direction of an increase in the ratio. This ratio is significantly higher in our more anxious than in our less anxious group, and since, as discussed above, there is reason to suppose that this ratio is determined by three mechanisms all acting in the same direction, it is to be expected that it would be a fairly sensitive indicator of anxiety.

Finally it should be mentioned that a similar effect was found in the case of responses to the electrical stimulus. The ratio fourth quarter shock response/first quarter shock response is greater in the more anxious group than in the less anxious group but the difference is not statistically significant. It is relevant also that in both groups the fourth quarter/first quarter ratio is much greater in the case of responses to shock than in the case of responses to light. It seems likely that changes in the " psychological " component of the response to shock are largely masked by the lower level reflex whose magnitude may be expected to depend upon the intensity of the stimulus.

Summary

The sudomotor responses (psychogalvanic reflexes) of a group of 36 psychiatric patients have been studied. The stimuli used were both physiological and psychological. The pain tolerance of all patients was measured.

Before the investigation each patient was assessed psychiatrically and rated for the level of clinical anxiety present. On this basis the 36 patients were divided into two equal groups, " less anxious " and " more anxious ".

The pain tolerance and the sudomotor responses to three types of stimuli—a deep breath, an electric shock, and a warning light—were not significantly different for the two groups. However, when the psychological responsiveness was considered in relation to the physiological responsiveness it was found that the former was relatively much greater in the more anxious group. This effect was marked and significant beyond the 0·1% level of confidence.

Some psychological determinants of autonomic responses are discussed, and it is concluded that under equal conditions of stress the more anxious group were distinguished by a tendency to form anticipatory sets which were accompanied by a relatively greater degree of autonomic disturbance.

We would like to express our gratitude to Dr. E. A. Carmichael, Professor J. Elkes, Dr. Eliot Slater, and Professor O. L. Zangwill, whose help and encouragement made this work possible. To Dr. P. Armitage we are indebted for statistical advice.

References

Bassett, M., and Ashby, W. R. (1954). *J. ment. Sci.*, **100**, 632.

Elithorn, A., Piercy, M. F., and Crosskey, M. A. (1951). *Journal of Neurology, Neurosurgery and Psychiatry*, **14**, 209.

——, ——, ——(1955). *Ibid.*, **18**, 34.

Haggard, E. A. (1949). *J. exp. Psychol.*, **39**, 378.

Lorenz, K. (1935). *J. Orn., Berl.*, **83**, 137–213, 289–413.

Malmo, R. B., and Shagass, C. (1950). *Arch. Neurol. Psychiat., Chicago*, **63**, 113.

Mowrer, O. H. (1938). *Psychol. Rev.*, **45**, 62.

Tinbergen, N. (1951). *The Study of Instinct*. Clarendon Press, Oxford.

BOOK REVIEWS

Sigmund Freud: On Aphasia (Translation by E. Stengel). (Pp. 105. 12*s.* 6*d.*) London: Imago Publishing Co. 1953.

This book was published in Vienna in 1891. This is its first English translation, and Dr. Stengel is to be congratulated on its clarity and lack of those verbal asperities which so often mar translations of technical monographs. The book is of historical interest as an early work of the originator of psychoanalysis. It already shows many aspects of the style that became familiar in Freud's later psychoanalytic works—pleasing use of language, the support of argument by analogy, and consideration of all the logical implications of any particular thesis. It was written at a time when the immense possibilities of localization of cerebral function were just being appreciated, but the author makes it clear, by logical argument from clinical facts, that an entirely anatomical approach to aphasia is not enough. While giving due weight to factors of localization, he pleads for a consideration of functional aspects also. This approach gives the book a more than historical value: indeed it reads—apart from occasional phrases which date it—almost as if it were written a generation after rather than before Head's *magnum opus*, and it is surprising and interesting to learn that Head apparently never read it.

As a review of the problems which are still integral to the study of aphasia it will reward the attention of neurologists, who will be glad to see that Hughlings Jackson's genius was clearly appreciated by Freud.

Multiple Sclerosis. By Douglas McAlpine, Nigel D. Compston, and Charles E. Lumsden. (Pp. viii + 304; 32 plates. 35*s.*) Edinburgh: E. & S. Livingstone. 1955.

This is an important addition to neurological literature. A large part of the book consists of a careful clinical study of over 1,000 cases of multiple sclerosis seen at the Middlesex Hospital Neurological Department during a period of 22 years. This contains much useful information for the clinician and, for example, includes an interesting study of the spread of plaques in the cervical cord, and of the results of careful questioning with regard to possible aetiological factors which seem to cause relapses in the disease. Familial cases are carefully reported. Prognosis as to disablement and life contain useful figures but the sections on treatment are unfortunately still vague and uncertain.

The chapters on pathology and the problems of aetiology are quite outstanding, and are based on Dr. Lumsden's important research work in this field. There are no specific nerve cell changes, and many of these are highly resistant to the effects of being in a plaque. The peculiarity of the break-up of the myelin sheath lies in its being confined to the area of plaque and seems to depend on a process of erosion or lysis from the outside of the plaque. It is not known whether a myelin sheath can be restored when the axon remains intact. Myelin sheaths are normally sheathed by the processes of oligodendrocytes, but these latter cells disappear early in the development of the plaque and are nowhere to be seen within the outer edge of the area of demyelination. The lesion may possibly always start in relation to a small blood vessel, but such relationship disappears as the plaque increases in size. Plaques are hardly ever completely quiescent for there is evidence of continued activity at the periphery of even the most sclerotic lesion.

With regard to the "allergic" encephalopathies, the disease differs from multiple sclerosis from start to finish. Recent work has shown that there is a steady turnover of myelin lipids and these are synthesized locally in the brain. In the process of demyelination, therefore, the local synthesis may be blocked, or the normal breakdown may be abnormally rapid. Finally, as a fitting climax to these stimulating pages, comes the hypothesis that the features of the plaque could all be explained by a process which has a selective effect on the oligodendrocyte.

IVth Symposium Neuroradiologicum

The meeting will be held in London from September 13 to 17. Registration will take place on September 12 at the University of London, Malet Street, W.C.1, where the scientific meetings will be held. Radiologists, neurologists, and neurosurgeons are particularly welcome.

Subjects for discussion include (1) cerebrovascular disease, (2) the localization of intracranial tumours by means of isotopes, (3) applications of stereotaxometry, (4) new techniques, and (5) various proferred papers on a variety of neuroradiological subjects.

Scientific and technical exhibitions are being held.

It is hoped to arrange a joint half-day session with the 2nd International Congress of Neuropathology which is being held simultaneously in London.

A full social programme has been planned including visits to places of interest for wives and families of members.

Those who cannot spare the whole time of the meeting are invited to become day members at a much reduced subscription rate.

Application forms and further information may be obtained from Dr. R. D. Hoare, Secretary, Symposium Neuroradiologicum, the National Hospital for Nervous Diseases, Queen Square, London, W.C.1.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Die Wirbelsaulenverletzungen und ihre Ausheilung. By Alfons Lob. (Pp. xii + 272; 149 illustrations, 16 tables. DM. 78.–.) Stuttgart: Georg Thieme Verlag. 1954.

The Cerebrospinal Fluid. By S. Lups and A. M. F. H. Haan; Introduction by Pearce Bailey. (Pp. xv + 350; 93 illustrations. 52*s*. 6*d*.) London: Cleaver-Hume Press. 1954.

Brain Mechanisms and Consciousness. A Symposium organized by The Council for International Organizations of Medical Sciences established under the joint auspices of U.N.E.S.C.O. and W.H.O. Edited by J. F. Delafresnaye. (Pp. xv + 556; illustrated. 42*s*. 0*d*.) Oxford: Blackwell Scientific Publications. 1954.

Développement Psycho-Moteur du Premier Age. By Cyrille Koupernik; illustrated by D. Harlé. (Pp. 197; 58 illustrations. Fr.frs. 500.–.) Paris: Presses Universitaires de France. 1954.

The Human Brain in Sagittal Section. By Marcus Singer and Paul I. Yakovlev. (Pp. v + 81; 46 illustrations. 45*s*. 0*d*.) Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles C. Thomas.

Modern Trends in Psychosomatic Medicine. By Desmond O'Neill. (Pp. xi + 375; 29 illustrations. 55*s*. 0*d*.) London: Butterworth. 1955.

Diencephalon. By Walter Rudolf Hess. (Pp. xii + 79; 33 illustrations. 25*s*. 0*d*.) London: William Heinemann. 1955.

Diseases of the Nervous System. 8th edition. By F. M. R. Walshe. (Pp. xvi + 357; 58 illustrations. 24*s*. 0*d*.) Edinburgh: E. & S. Livingstone. 1955.

Psychosurgery and the Self. By Mary F. Robinson and Walter Freeman. (Pp. ix + 118. $3.00.) New York: Grune & Stratton. 1954.

The Pyramidal Tract. By A. M. Lassek. (Pp. v + 167. 34*s*. 0*d*.) Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles C. Thomas. 1954.

Essentials of Abnormal Child Psychology. By Ernest Harms. (Pp. xiv + 265; 45 illustrations. $5.00.) New York: Julian Press Inc. 1954.

The Visual Fields. By Brodie Hughes. (Pp. ix + 174; 158 illustrations. 35*s*. 0*d*.) Oxford: Blackwell Scientific Publications. 1954.

Child Psychology, 4th ed. By Arthur T. Jersild. (Pp. xii + 676. 42*s*. 0*d*.) London: Staples Press Ltd. 1955.

Physiologie du Système Nerveux Central, 2nd ed. By Georges Morin. (Pp. 354; 95 illustrations. Fr.frs. 2,300.–.) Paris: Masson & Cie. 1955.

Psychomotor Aspects of Mental Disease. By N. E. King. (Pp. xiv + 185. 28*s*. 0*d*.; $3.50.) London: Oxford University Press; Cambridge (Mass.): Harvard University Press. 1955.

Neurocirugia, Vol. X. Published by Dr. Alfonso Asenjo, Santiago (Chile). 1954.

Neurology, 2nd ed. By S. A. Kinnier Wilson, edited by A. Ninian Bruce, in three volumes. (Pp. xxix + 2060 + Index; 279 illustrations. £10 10*s*. 0*d*. per set; £3 10*s*. 0*d*. per volume). London: Butterworth. 1954.

Hyperostosis Cranii. By Sherwood Moore. (Pp. xxii + 226; 107 illustrations. 75*s*. 0*d*.) Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles C. Thomas. 1955.

Correlative Neurosurgery. By Edgar A. Kahn, Robert C. Bassett, Richard C. Schneider, and Elizabeth Caroline Crosby. (Pp. xv + 413; 235 illustrations. £7 0*s*. 0*d*.) Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles C. Thomas. 1955.

Die Chirurgie der peripheren Nerven. By H. Nigst; Introduction by R. Nissen. (Pp. viii + 196; 104 illustrations. DM. 29.70.) Stuttgart: Georg Thieme Verlag. 1955.

A Textbook of Neurology. By H. Houston Merritt. (Pp. 746; 181 illustrations, 128 tables. 90*s*. 0*d*.) London: Henry Kimpton. 1955.

The Psychological Variables in Human Cancer. A Symposium presented at the Veterans Administration Hospital, Long Beach, California, on October 23, 1953. Edited by Joseph A. Gangerelli and Frank J. Kirkner. (Pp. 135; 10 illustrations. 22*s*. 6*d*.) London: Cambridge University Press. 1955.

Die Cervikalen Vertebral-Syndrome. Edited by F. Reischauer. (Pp. 71; illustrated. DM. 7.80.) Stuttgart: Georg Thieme Verlag. 1955.

The Management of Acute Poliomyelitis. By C. P. Stott and M. Fischer-Williams; Foreword by W. Ritchie Russell. (Pp. xii + 99; 43 illustrations. 12*s*. 6*d*.) Edinburgh and London: E. & S. Livingstone. 1955.

Research Fellowships in the Field of Multiple Sclerosis and Allied Diseases

The National Multiple Sclerosis Society has established a limited number of fellowships to encourage promising students and scholars to enter the field of research related to multiple sclerosis and the demyelinating diseases.

Fellowship candidates are free to elect a training institution and sponsor of their own choice.

Applications may be secured by writing to: Harold R. Wainerdi, M.D., Medical Director, National Multiple Sclerosis Society, 270 Park Avenue, New York 17, N.Y.